Keeping Medical Devices Safe From

ELECTROMAGNETIC INTERFERENCE

Life Support Equipment Area
Cellular Telephones Are PROHIBITED
OTC Options: Treating Acne

Though severe acne requires a doctor's attention, milder cases may respond to treatment with nonprescription products. But FDA has raised concerns about possible hazards from the active ingredient—benzoyl peroxide—in some of those products.

Keeping Medical Devices Safe from Electromagnetic Interference

As wireless communications devices, such as cellular phones, become more common in the health field and other areas of life, the energy they emit may interfere with similar energy from medical devices. FDA is looking for ways to lessen this problem.

New Choices for Coping with Genital Warts

Alpha interferon, laser surgery, and topical drugs have joined other treatments for genital warts, a virus-caused sexually transmitted disease contracted by about half a million Americans a year. But no available therapy provides a perfect solution.

Public Affairs Specialists: FDA's Walking Encyclopedias

FDA's public affairs specialists across the country act as media representatives, teachers, and advisors. They routinely answer questions on a multitude of subjects, ranging from food labeling to condoms, from seafood safety to proper medicine use.

Testosterone: Key to Masculinity and More

The same hormone that differentiates a fetus into a boy continues its influence throughout a man's lifetime. Forms of testosterone are approved as drugs to treat male hormonal problems and are also being investigated for other medical uses. Testosterone also plays a role—though a far smaller one—in women's health.

Updates

Notes
**OTC Spermicide Rule Proposed**

The public has until June 5 to submit written comments on an FDA-proposed rule concerning over-the-counter (OTC) spermicide products. The rule, published in the Feb. 3 Federal Register, asks that manufacturers submit a new drug application (NDA) for each individual product demonstrating that the final formulations of the products are effective contraceptives.

FDA has concluded that the active ingredients in marketed spermicides generally are safe, but their effectiveness in final product formulations is highly variable.

Spermicide contraceptives are available as foams, gels, creams, films, and suppositories. The active ingredients, nonoxynol-9 and octoxynol-9, work by forming a physical and chemical barrier to sperm in the vagina.

There is evidence that some OTC spermicide formulations can lose effectiveness as contraceptives during use. For this reason, clinical data are needed to ensure their effectiveness.

Vaginal contraceptives have also been associated with vaginal irritation, which may play a role in transmitting sexually transmitted diseases (STDs). Therefore, the proposal asks manufacturers to collect information on irritation during clinical trials, and to include this data in the NDA.

The proposal does not cover claims for prevention of STDs, including AIDS. However, FDA encourages manufacturers to evaluate products for prevention of infectious diseases. Separate clinical trials must be conducted before claims of disease prevention can be made.

Marketing status of OTC spermicides would not be immediately affected by the proposed rule. However, to ensure continued availability after a final rule is published, FDA encourages manufacturers to contact the agency as soon as possible so that clinical studies can be conducted and applications approved as quickly as feasible.

Products that fail to meet the requirements of the final rule would be considered unapproved new drugs and subject to regulatory action.

Comments should be addressed to: Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

**Hepatitis A Vaccine Licensed**

The first vaccine to prevent the highly contagious hepatitis A infection received FDA licensing last Feb. 22.

Manufactured under the trade name Havrix, the vaccine is indicated for international travelers, people living in or relocating to areas where the disease is endemic, some military personnel, and certain high-risk individuals such as some hospital and laboratory personnel. An FDA advisory committee reviewed safety and efficacy data in January 1994 and recommended the vaccine for selected groups.

The vaccine was 84 percent effective in a clinical trial of more than 19,000 school children in Thailand. Adverse reactions were mild and included redness, hardness and swelling at the injection site, fatigue, fever, malaise, and nausea. The trial was sponsored by the U.S. Armed Forces Research Institute for Medical Sciences and the Thai government.

Official reports in 1992 cited more than 23,000 cases of hepatitis A in the United States, but annual estimates of infection range from 100,000 to 150,000.

Hepatitis A usually is spread by contaminated food or water or by close contact with an infected person. The disease also can be contracted by eating raw or undercooked shellfish harvested from contaminated waters.

Outbreaks of the infection sometimes occur in institutional settings such as day-care centers. Military personnel living in field conditions, crowded barracks, and certain geographic areas are at high risk for the disease.
Ma Huong and Kola Nut Combination Can Be Deadly

Consumers should not buy or ingest Nature’s Nutrition Formula One products labeled as containing Ma huang (ephedrine) and kola nut, FDA warns. The agency received more than 100 reports of illness associated with the product in 1994, as well as several deaths. Reported reactions include serious, life-threatening conditions such as irregular heartbeat, heart attack, stroke, seizures, hepatitis, and psychosis. Also reported are minor temporary conditions such as dizziness, headache, and gastrointestinal distress.

Labels of the potentially dangerous products list both Ma huang and kola nut and make either of the following usage statements: “Adult Food Supplement Take 1 to 3 capsules at 10:00 AM & 3:00 PM,” or “Adult food supplement: one to two capsules mid-morning and mid-afternoon.”

FDA and nonagency medical experts determined that the combination of Ma huang (a source of ephedrine) and kola nut (a source of caffeine) can cause severe injury to people even under conditions of usual or recommended use. Ephedrine is an amphetamine-like chemical that acts as a stimulant.

FDA’s warning is limited to versions of Nature’s Nutrition Formula One that contain both Ma huang and kola nut. The manufacturer, Alliance U.S.A., advised FDA that it had reformulated the product to remove kola nut. Although the FDA warning does not apply to the new version of the product, at press time in early March, FDA was continuing to evaluate the safety of ephedrine-containing products made or distributed by Alliance U.S.A. and other companies.

Infertility Drug Approved

A drug to treat infertility in women, Humegon (menotropins for injection), was approved by FDA Sept. 1, 1994. Limited quantities of the drug, manufactured by Organon Inc., West Orange, N.J., have been available since March.

Two similar fertility drugs, Pergonal, which is the same drug generically as Humegon, and Metrodin (urofollitropin for injection), have recently been in short supply due to production decisions by the drugs’ manufacturer, Serono Laboratories Inc.

Last December, Serono told health professionals and distributors that it was reserving the remaining stocks of the drugs for patients already receiving treatment. If such patients ran out of their supply, doctors could request an additional supply by calling Serono at (1-800) 283-8088.

If the necessary drugs were unavailable to doctors from Serono or Organon, FDA announced it would not object if patients, working closely with their doctors, temporarily imported the drugs for personal use from an alternative source. Unless it was medically necessary, however, doctors were advised not to treat new patients until the supply of approved drugs increased.

Serono, a Swiss firm, has U.S. headquarters in Norwell, Mass.

Treatment IND for Advanced Pancreatic Cancer Drug

An investigational treatment for patients who have advanced pancreatic cancer but are not candidates for surgery was granted Treatment IND status by FDA last February.

Two clinical trials conducted by the drug’s sponsor, Eli Lilly and Co., have suggested that gemcitabine (Gemzar) may effectively treat this cancer. The studies measured tumor shrinkage, survival, and an overall estimate of clinical benefit (pain and ability to function). Both studies showed a small rate of tumor shrinkage (about 7 percent) and about a 25 percent rate of clinical response in the patients. One study showed a small improvement in median survival time (about one and a half months).

The agency’s Treatment IND regulations allow drug developers to provide earlier and wider access to investigational therapies for patients with serious diseases for which there is no satisfactory alternative treatment.

About 27,000 people in the United States were diagnosed with pancreatic cancer in 1994. Generally not causing...
symptoms until late in the disease, it is among the most difficult cancers to treat and is rarely curable. No therapies have been approved specifically for pancreatic cancer.

In clinical tests, the major side effects of gemcitabine have been a decrease in white blood cells (which increases susceptibility to infection), risk of excessive bleeding, and elevation of liver enzymes. Nausea, vomiting, rash, flu-like symptoms, breathing difficulties, and traces of blood and protein in the urine were also reported.

Physicians interested in entering patients in the Treatment IND program may call (1-800) 621-7111 for more information.

Blood Corporation Submits Correction Plan

A large blood collection corporation submitted a corrective action plan to FDA after the agency notified the firm it intended to revoke its license unless it acted immediately to correct significant deficiencies uncovered by FDA inspections.

United Blood Services Blood Systems Inc. (UBS) of Scottsdale, Ariz., was informed of FDA's decision last February in a letter requiring the firm to submit a comprehensive correction plan within 30 days. UBS has 18 licensed locations, 50 donor centers, and numerous mobile operations in 12 states.

FDA inspected all licensed UBS blood establishments and the firm's corporate headquarters between May and December 1994. Significant deficiencies affecting the corporation's entire operation were found in testing procedures, donor deferral practices, computer operations, look-back notification procedures, and error and accident investigation and reporting practices.

FDA initiated revocation procedures based on the firm's continuing deficiencies and its inability to correct serious problems identified earlier. Two of UBS's Texas facilities voluntarily surrendered their licenses recently in response to FDA actions. In 1993, FDA notified a Texarkana facility of the agency's intent to revoke its license, and in 1994, FDA suspended the license of a Lubbock facility. Both facilities remain closed.

Curious George Helps Kids Check Out Food Label

In the past, curiosity always meant trouble for Curious George, the monkey from the popular children's book series. But now this trait is helping Curious George help children. In a new public service advertising campaign aimed at children, the monkey checks out the new food label.

The campaign, developed with support from FDA and its parent, the Department of Health and Human Services, is the creation of KIDSNET, a Washington, D.C.-based organization specializing in children's education. By using puppetry and state-of-the-art video production techniques, the campaign makes the food label real and relevant to children ages 4 to 10 through radio and television spots in English and Spanish. KIDSNET has also produced a companion kids-oriented brochure.

The goal of the campaign is to make children more aware of the nutrition facts label, and encourage children to share their knowledge with their whole family.

"Children can be the most persuasive teachers we ever encounter," says David A. Kessler, M.D., commissioner of FDA. "Many of us learned to 'buckle up' and recycle from our sons and daughters, nieces and nephews."

Children—even those who are very young—make decisions about food purchases and consumption, according to focus group research conducted for KIDSNET. Further, the data show that children are interested in food topics and want more information, especially through entertainment sources such as television and radio.

Supporting these findings, marketing research reveals that children exert the greatest impact on family purchases of foods and beverages. Of the estimated $147.4 billion of household purchases that children influence, $99.7 billion relates to food items, according to KIDSNET.

The television spots will be aired during children's programming on 55 commercial and cable networks, including

Funding for the campaign was initially underwritten by the Robert Wood Johnson and the Kaiser Family foundations with additional support from FDA. The TV spots were funded by the Florida Department of Citrus, and the companion brochure was provided by Iron Kids Bread.

For a free copy of the brochure, which explains the different parts of the nutrition facts label through games and pictures, write to KIDSNET, Consumer Information Center, Pueblo, CO 81009.

**Computerized Food Info Center**

As part of a national campaign to reduce the risk of food-borne illness, several federal agencies have established a computerized education information center accessible 24 hours a day.

The Foodborne Illness Education Information Center was formed this year by FDA, the U.S. Department of Agriculture’s Food Safety and Inspection Service and Cooperative State Research, Education and Extension Service, and the National Agricultural Library (NAL). The center is in NAL’s Food and Nutrition Information Center.

The center helps educators, trainers and consumers locate educational materials on preventing food-borne illness. It maintains a database of such materials that includes computer software, audiovisuals, posters, games, teachers’ guides for elementary and secondary school education, and training materials for employees of retail food stores and food service establishments.

The database can be accessed through the Internet by downloading from the Food and Nutrition Information Center gopher: First gopher to “gopher.nalusda.gov.” Choose “NAL Information Centers,” then “Food and Nutrition Information Center,” then “USDA/FDA Foodborne Illness Education Information Center.” Or, telnet to your favorite gopher, choose “All the Gophers in the World,” then “Gopher Servers in the USA,” then “Maryland,” then “Food and Nutrition Information Center,” and proceed as above.

Consumers can get a report of the database’s contents by sending a 5½” or 3½” floppy disk to the Foodborne Illness Education Information Center.

Reports also can be accessed seven days a week, 24 hours a day through NAL’s electronic bulletin board, ALF. The modem numbers are (301) 504-6510, (301) 504-5111, (301) 504-5496, and (301) 504-5497. Modern settings are data bits: 8, stop bit: 1, parity: none, duplex: full.

For more information or to contribute to the database, contact Cindy Roberts, information specialist, USDA/FDA Foodborne Illness Education Information Center, Food and Nutrition Information Center, National Agricultural Library/USDA, Beltsville, MD 20705-2351; facsimile (301) 504-6409; E-mail: croberts@nalusda.gov.

**Special Issue on New Drug Development**

The second edition of the FDA Consumer special issue on new drug development is now available. To order copies of From Test Tube to Patient: New Drug Development in the United States (stock number 017-012-00371-1), write to Superintendent of Documents, P.O. Box 371954, Pittsburgh, PA 15250-7954. The 67-page anthology is $5 per copy ($6.25 foreign). Include stock number. GPO accepts payment by check payable to Superintendent of Documents, by GPO account number, and by VISA or MasterCard with account number, credit card expiration date, and authorizing signature.

**Correction**

A caption in “Labeling Rules for Young Children’s Foods” in the March 1995 FDA Consumer incorrectly stated the age group. The top caption on page 16 should have read “Nutrition Label for Foods for Children Under 2.”

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

The very word is enough to halt most teenagers in their tracks. Yet rare is the adolescent who can escape the skin disorder completely.

"It is almost universal," says Alan R. Shalita, M.D., chairman of the dermatology department at State University of New York. Shalita and other experts estimate that 85 percent of the U.S. population between the ages of 12 and 25 suffers from some form of acne vulgaris, the medical term for the condition.

Though acne often is a simple case of pimples, it sometimes can erupt as unsightly pus-filled sores with the potential to disfigure. Acne may fracture self-esteem in the teen years, but this

*FDA's proposed labeling changes on benzoyl peroxide products warn users to avoid unnecessary sun exposure and to apply a sunscreen if going outdoors.*
FDA officials are concerned about what happens when skin treated with benzoyl peroxide is exposed to the sun.

dermatological rite of passage generally is history by early adulthood. But not always. Cases of the ailment occur occasionally in pre-teens and in older adults. Sometimes women experience acne flare-ups at certain stages of the menstrual cycle or after discontinuing oral contraceptives. Experts say stress and heredity also can play a part.

The American Academy of Dermatology says it's a good idea for acne sufferers to check with a dermatologist to ensure the skin condition really is acne. Rashes from other sources such as makeup and oral medicine can create acne-like symptoms.

Severe acne requires a doctor's attention to prevent permanent scarring. (See "Acne Agony" in the July-August 1992 FDA Consumer.) But milder cases often yield to treatment with over-the-counter (OTC) products. Dozens of products are available in varying strengths as creams, lotions, gels, and cleansers. In its review of OTC drugs, the Food and Drug Administration approved sulfur, resorcinol, and salicylic acid for OTC treatment of acne. The agency determined that more safety studies are needed for another ingredient, benzoyl peroxide. All these ingredients were on the market before 1972, when FDA began a review of OTC drug products.

Some Unanswered Questions

Benzoyl peroxide products have been sold for more than 25 years. FDA and the dermatological community have long considered the drug to be an effective nonprescription acne medicine. But FDA officials are concerned about what happens when skin treated with benzoyl peroxide is exposed to the sun. Study data are inconclusive at this time.

Scientists call chemicals and radiation that can start tumor growth "initiators." The sun's ultraviolet light is a known initiator. Substances that increase tumor development when an initiator is present are called "promoters." Benzoyl peroxide is considered a promoter.

Researchers have observed that benzoyl peroxide has a tumor-promoting effect in mice exposed to a chemical initiator. They don't know yet what effect the sun may have specifically on skin treated with benzoyl peroxide. Until research can establish or disprove a link, FDA plans to require extra warning and direction statements on benzoyl peroxide product labels. The agency published a Federal Register notice on Feb. 17 to solicit comments on its proposed labeling changes. Deadline for comments is May 18.

Though studies in mice showed that benzoyl peroxide did not cause the growth of tumors initiated by the sun, these studies did not resolve the issue, say FDA officials. The research used an inadequate number of mice and did not show conclusively whether benzoyl peroxide actually increased tumors. Another study in progress with more than 100 mice should allow scientists to make more valid conclusions.

Researchers also are conducting tests to determine what effect benzoyl peroxide has on mice and rats for the lifetime of the animal. When these tests are completed, FDA will evaluate results and decide how the information will affect the use of benzoyl peroxide products.

Other existing studies further cloud the association between the drug and cancer. For example, a recent Canadian survey-type study queried benzoyl peroxide users to find out if they had developed skin cancer. Results showed that
Experts estimate that 85 percent of the U.S. population between the ages of 12 and 25 suffers from some form of acne.

users of these products did not have a higher risk of developing tumors or cancer. Though the study generally was well-designed and furnished useful information, FDA officials say, it did not group subjects for skin cancer risk by duration of use and time since last use of the drug. The survey also did not consider the reasons for benzoyl peroxide therapy and users’ ages. FDA found the study to be limited in how well it can determine the effects of benzoyl peroxide over long periods for persons who have greater exposure in locations where the sun is more intense than in Canada.

Benzoyl peroxide continues to be available over the counter and by prescription in a number of strengths while researchers perform the additional studies. FDA considers benzoyl peroxide safe for treating acne while tests proceed.

The proposed warning is in two parts:

- In boldface type as the first sentence under the “Warnings” heading is the statement: “When using this product, avoid unnecessary sun exposure and use a sunscreen.”
- In the “Directions” section of the labeling is the statement: “If going outside, use a sunscreen [the preceding sentence is in boldface type]. Allow (product name) to dry, then follow direc-
That’s Oil, Folks!

Sebaceous glands in hair canals (follicles) produce an oily substance called sebum. Normally, sebum empties onto the skin surface and is washed away. But sometimes hormones produced in the adrenal glands trigger production of excess sebum, which creates plugs in follicle openings. If the plug breaks through the skin, appearing darker than the skin, it is called a blackhead, or open comedo. If the plug is below the skin surface, it is called a whitehead, or closed comedo.
Severe acne requires a doctor’s attention to prevent permanent scarring.

Acne starts when glands in hair canals (follicles) just below the skin’s surface make an oily substance called sebum. Normally, sebum empties through follicle openings onto the skin surface, where it is washed away. In people of both sexes who get acne, the adrenal glands secrete male-type hormones that trigger excess production of sebum. Experts believe sebum stimulates the lining of the follicle wall, causing cells to shed, stick together, and plug up the follicle opening. If this plug remains below the surface, it is usually light in color and called a whitehead, or closed comedo. An enlarged plug that emerges from the follicle typically has a dark tip and is called a blackhead (an open comedo). The mixture of cells and oil creates a breeding ground for bacteria, which produce chemicals that can break down the follicle wall and create pimples or more serious inflammation.

OTC drugs work in similar ways. Benzoyl peroxide, resorcinol, salicylic acid, and sulfur are all “peeling agents,” technically known as keratolytics. They cause a superficial irritation and drying that helps the body loosen plugs in the follicle and slough off dead cells. These drugs also keep bacteria from forming in the follicle. This, in turn, reduces fatty acids that contribute to plugs. A number of OTC acne drug products combine sulfur with resorcinol.

In severe acne cases, doctors prescribe other drugs either separately or in tandem with OTC preparations. The American Academy of Dermatology cautions against scratching or squeezing acne sores, which can lead to more inflammation and scarring. The academy offers a free brochure about acne and its treatment. For a copy, send a stamped, business-size envelope to: American Academy of Dermatology P.O. Box 681069 Schaumburg, IL 60168-1069.

John Henkel is a staff writer for FDA Consumer.
Between 1979 and 1993, FDA received reports of more than 100 suspected incidents of EMI with medical devices.

How could a nurse work without a beeper? An ambulance without a two-way radio? A doctor without a cellular phone?

Today's medical professionals rely heavily on wireless communication devices to help them do their jobs efficiently. And yet the proliferation of such gadgetry is not without its problems. Increasingly, medical and communications devices may be at odds with each other.

The problem is electromagnetic interference (EMI), and it's becoming a growing concern among hospital staffs, electronics manufacturers, and the Food and Drug Administration. Every electrical device emits electromagnetic energy. This energy can interfere with other devices the way a hair dryer creates “snow” on a nearby television.

Most of the time the problem is merely annoying. For example, EMI could cause static on the screen of a hospital computer. But whenever anything interferes with a lifesaving medical device like a pacemaker or an apnea monitor, the results can affect the patient.

Between 1979 and 1993, FDA received reports of more than 100 suspected incidents of EMI with medical devices. Because the interference was almost always fleeting and difficult to reproduce, most of those reports have not been verified or duplicated in laboratory settings. Nevertheless, FDA suspects EMI caused most of them, including the following:

- A pacemaker failed during an ambulance ride while the two-way radio was in use.
- A man in a powered wheelchair was seriously injured when his chair rode off a cliff at high speed. He was several miles from a radio tower and three blocks from a busy road, where mobile radios were likely in use.
- A pulse oximeter machine displayed a pulse rate and oxygen level on a dead body when a telemetry receiver that was part of the system was placed too close to the body.
- A fetal heartbeat detector picked up local radio and CB broadcasts instead of the baby's heartbeat.

As wireless technologies proliferate and the airways become more crowded, EMI is bound to increase. However, FDA, the medical device manufacturers, and members of the electronics industry are taking steps to minimize the danger it poses.

It will not be easy to make all medical devices immune to unwanted electromagnetic waves. The exposure,
“There’s really no place to get away from electromagnetic waves. They’re in the room, they’re in the air.”
—Don Witters, FDA physicist

frequency, location, orientation, and design of a device all influence whether it will experience EMI.

“It’s a complex phenomenon, and we don’t yet know how it occurs in some cases,” says Don Witters, an FDA physicist and chairman of an agency working group examining the problem.

“There are large uncertainties here. You can make a device immune to a certain level, but it really depends on several complex things interacting.”

Clutter on the Airways

Sources of possible electromagnetic interference increase every year. Citizens Band radios, cellular telephones, wireless computer links, microwave signals, radio and television broadcast transmitters, pagers, and many other machines emit electromagnetic waves that could interfere with other devices.

For practical purposes, it’s impossible to stop electromagnetic waves completely at their source. Modern society has become much too dependent on the convenience of instant communication. And since medical devices themselves often emit electromagnetic waves, using several machines at once in a hospital room can cause problems.

It is much more feasible to build electromagnetic compatibility (EMC) into new medical devices, so they can operate accurately in an environment flooded with electromagnetic waves, and so they don’t give off any more waves than necessary.

“There’s really no place to get away from electromagnetic waves. They’re in the room, they’re in the air,” says Witters. “Even the body itself is electrical and acts as a transmitter for energy. Your body can generate electrostatic energy by walking across a wool rug on a winter day.”

In an effort to investigate EMI problems with medical devices, FDA has already examined a few devices that are especially sensitive to electromagnetic waves.

Apnea monitors, for example, can be very sensitive. Used on premature babies and adults with sleeping disorders, the monitors are supposed to sound an alarm if the patient stops breathing while asleep.

In 1987, a physician in Nebraska reported to FDA that monitors in some neighborhoods of Omaha would not work properly. FDA tested monitors both at the site and in the laboratory and found that certain models are, indeed, very sensitive to electromagnetic waves.

The monitors can mistake low levels of modulated electromagnetic waves for breaths, therefore failing to sound the alarm if the patient stops breathing. Some monitors were so sensitive that a person walking across the room changed the waves in the room enough to fool the monitor.

FDA asked the manufacturer of the most sensitive monitor to recall the device. This machine malfunctioned when the monitor or the cables were touched or when an electrostatically charged fabric was waved over it.

While not as sensitive as the apnea monitors, powered wheelchairs may also encounter EMI-related problems. FDA has tested these and powered scooters in its laboratories after receiving a number of reports of the machines malfunctioning.

FDA engineers found that the wheelchairs’ brakes would release and the wheels would begin turning in relatively low-strength electromagnetic fields. A police radio held about a meter away (3 feet, 4 inches) could cause some wheelchairs to move.

In response to this problem, in May 1994 FDA asked wheelchair manufacturers to ensure that all new chairs be at least reasonably immune to EMI (FDA recommends an immunity of 20 volts per meter), that they be labeled with the immunity level, and that purchasers be warned about the possibility of EMI and how to avoid it. FDA has also been working with the Rehabilitation Engineering Society of North America to develop EMC standards for wheelchairs. The goal is to increase the amount of electromagnetic waves the chairs can withstand without malfunctioning (that is, increase the immunity to EMI).

Today, FDA requires all new powered wheelchairs, respiratory devices, and
The popular television series “ER” ran an episode last fall about a cellular phone wreaking havoc in a hospital emergency room. The electromagnetic waves radiating from someone’s phone caused a powered wheelchair to spin out of control and a woman’s implant cardiac defibrillator to fire without cause.

This fictional situation is based on a real-life problem. Some European hospitals have already banned cellular phones from their buildings, and FDA has encouraged hospitals in the United States to take such action if warranted.

But that doesn’t mean these phones should be outlawed everywhere. Though a popular target for blame, cellular phones are likely a small part of the problem, says Don Witters, an FDA physicist and chairman of an agency working group examining the problem.

Cellular phones generate a very small amount of the total electromagnetic waves in the atmosphere. But because of their mobility, these phones have the potential to get closer to most medical devices than, say, a radio station transmitter on top of a hill.

Patients and doctors who routinely use sensitive medical devices should be aware of the problem and consider keeping cellular phones away from their equipment.

The Cellular Telecommunications Industry Association, concerned about the problem electromagnetic interference poses for cellular phones, has given seed money to start a research center at the University of Oklahoma to explore the issue. ■

—R.D.W.
It will probably be easier to design and build new devices that are electromagnetically compatible than to retrofit old ones. Implanted pacemakers to meet rigorous FDA guidelines for EMC before they can be approved. FDA plans to develop guidelines for other medical devices as needed. It will probably be easier to design and build new devices that are electromagnetically compatible than to retrofit old ones. Some devices can be protected more easily than others. A large x-ray machine or MRI machine, for example, can be placed in a shielded room to protect it from interference and limit its emissions from affecting other devices. A pacemaker, on the other hand, travels with the patient. It must be able to sense tiny electrical impulses from the patient's body without interference from other energy waves in the area.

What Consumers Can Do
Consumers and health professionals who use sensitive medical devices can take steps on their own to protect themselves from unwanted interference. FDA recommends the following:

- Be aware that EMI can cause steady, momentary or intermittent disruption of the performance of many medical devices.
- Follow the recommendations of the device manufacturer for avoiding EMI.
- Purchase equipment that conforms to EMC standards. New apnea monitors, pacemakers, respiratory devices, and powered wheelchairs must meet certain EMI guidelines. Older equipment may not meet them. Not all products are labeled with immunity levels or whether they meet EMC standards. The user may need to contact the manufacturer for that information.
- As much as possible, try to keep known sources of interference (such as cellular phones and hand-held transceivers) from coming too close to patient monitors and other sensitive electronic medical devices.
- When an EMI problem is suspected, contact the manufacturer of the medical device for assistance. Local clinical engineers (often employed as equipment technicians in hospitals) may also be able to identify and correct the problem.
- Report the device problem to FDA's MedWatch Program (1-800-FDA-1088) and note if the problem is believed to be linked to interference from a recognizable source of electromagnetic energy in the vicinity.

"FDA certainly has made this a priority," says Witters. "We're beginning to address this across a whole range of devices and that will take some time to do."

In the meantime, he says, consumers should report any problems by calling FDA's MedWatch Program and should make a conscious effort to keep sensitive medical devices away from transmitters like cellular phones and walkie-talkies. Says Witters, "The key in dealing with this is awareness."

Rebecca D. Williams is a writer in Oak Ridge, Tenn.
NEW CHOICES
FOR COPING WITH

Genital Warts

by Ricki Lewis, Ph.D.

It may not grab as many headlines as AIDS and herpes, but genital warts, another sexually transmitted disease, is also a current concern. Half a million new cases of genital warts are diagnosed in the United States each year. Visits to physicians for treatment of genital warts have increased tenfold since 1986, perhaps because of increased awareness of sexual health issues.

Technically known as condyloma acuminata, genital warts are small growths, resembling cauliflower, that occur on or near the genitals. Like other
Preventing spread of human papilloma virus is difficult, because many people have the virus without visible signs of it.

warts, the genital variety is caused by a virus, called human papilloma virus (HPV). This virus comes in 60 forms, two of which account for nearly all cases of genital warts.

The wart itself is actually "the tip of an iceberg," says Katherine Stone, M.D., medical epidemiologist with the division of sexually transmitted diseases at the national Centers for Disease Control and Prevention in Atlanta. This is because the virus lurks in cells of the normal-appearing skin around the visible wart, and also possibly in other urogenital areas. The viral nature of the condition also has important implications for transmission and treatment.

Sexual Transmission

Because active virus is on the genitals, sexual contact can spread the infection. Studies show that 60 to 90 percent of people whose partners have visible warts also have warts within three months.

However, many people may harbor this virus and not know it. The virus may infect cells but not cause warts for many years, erupting into visible lesions when the immune system is suppressed. Several studies of women receiving routine Pap smears, which can reveal HPV infection, show that many women without a recent history of exposure harbor the virus, suggesting that it may have been acquired earlier.

The viral nature of genital warts suggests that anti-viral therapies may be effective. Standard treatments burn, scrape, freeze, or use a laser to remove affected tissue. A newer treatment, alpha interferon, attacks the virus, the underlying source. In 1988, the Food and Drug Administration licensed alpha interferon to treat genital warts in patients who have not been helped by other therapies.

"Interferon is an anti-viral agent, and warts are caused by viruses. It also has other effects—it is an anti-proliferative, blocking cell division, and has immunomodulatory effects. It is an effective therapy," says David Finbloom, M.D., chief of the Laboratory of Cytokine Research at FDA. In development are several biologic agents that attack the virus' genetic material. Although these new approaches make scientific sense, whether or not they offer better relief than traditional treatments remains an important question.

A genital wart may appear externally on the genitalia, in the anal area, internally in the upper vagina or cervix, and in the male urethra. The lesion is typically raised and pinkish. This condition may produce no symptoms at all, or cause itching, burning, tenderness, pain during intercourse, or frequent urination.

But because of a wart's location and sexual mode of transmission, it may cause emotional and social problems. "Genital warts can inflict extreme psychological turmoil, and patients often feel embarrassed, angry, and even guilty," says Robert Brodell, M.D., head of the dermatology section, Northeastern Ohio Universities College of Medicine in Warren, Ohio. He has a large private practice and uses many techniques to treat genital warts. Although the warts themselves may not hurt, treatment does, and the high frequency of recurrence, even with treatment, can be very frustrating, he adds.

Concern about genital warts has increased because of an association between HPV and genital cancers. But cancer risk is not elevated for people with visible genital warts, says CDC's Stone. Of the 60 known types of HPV, five are seen in nearly all surface cancers of the cervix, vagina, vulva, anus, penis, and perianal area—but these are not the forms of the virus that cause visible warts. Cancer is linked to types 16, 18, and 31; genital warts to types 6 and 11.

Risk Factors

Anyone who has ever had sex is at risk for harboring HPV. The virus seems to cause visible lesions when a person's immune system is suppressed, but may flare up even without an obvious trigger. This may occur because of illness (particularly other sexually transmitted diseases), or from taking certain drugs, such as cancer chemotherapy or drugs to prevent rejection of an organ transplant. Deficiencies of folic acid and vitamin A also may trigger genital warts. Smoking raises risk twofold, partly because nicotine byproducts attack immune system cells in the cervix, says Stone.

Preventing spread of HPV is difficult, because many people have the virus without visible signs of it. "Condoms will not completely prevent transmission of genital warts. This is a virus that may exist outside the area protected by a condom—even if the warts are not visible," says Marcia Bowling, M.D., clinical assistant professor in the division of gynecologic oncology at the University of Cincinnati.

Diagnosis

Finding a cauliflower-like growth on the genitals is reason to see a dermatologist, urologist or gynecologist, who can tell if it is genital warts or a different kind of growth, such as a cancer or ulcer. A gynecologist may use a type of microscope called a colposcope to examine a woman's cervix to see if there are internal outbreaks.

When acetic acid (vinegar) is swabbed on the cervix, HPV lesions appear white. Colposcopy can be valuable in detecting flat lesions that are not visible to the unaided eye, but only two-thirds of white areas seen in a colposcope are due to HPV infection. Sampling cells with a
People with genital warts have a variety of treatments to choose from, but none is a perfect cure, and all have side effects.

biopsy and testing for HPV genetic material may be necessary to confirm a diagnosis.

Treatment

People with genital warts have a variety of treatments to choose from, but none is a perfect cure, and all have side effects. The treatments also vary widely in cost. In the March 1995 issue of Clinical Infectious Diseases, Stone writes that several treatment studies have demonstrated that warts treated with placebo preparations completely regressed within three months in 10 to 30 percent of patients, and that no studies have followed persons with warts longer than five months to assess spontaneous regression. The problem, of course, is that there is no way to know who the lucky patients will be.

Genital wart treatments fall into three categories—prescription topical preparations that destroy wart tissue; surgical methods that remove wart tissue; and biological-based approaches that target the virus causing the underlying condition. (Each treatment must be applied to individual warts—none is taken systemically.)

FDA has approved Condylox (podofilox) as a topical treatment for genital warts. Some doctors also prescribe Podocon-25 and Podofin (podophyllin), which are approved for other uses.

Podocon-25 and Podofin are made from resin of the mandrake plant, or May apple. A physician applies the drug to warts, where it causes the skin to ulcerate. Typically the drug is left in place for only 30 to 40 minutes the first time to see how the patient reacts. In subsequent treatments, podophyllin is left on for up to four hours but no longer, or surrounding skin may ulcerate. Side effects include pain, redness, itching, burning, and swelling of the treated area.

Human papilloma virus, which causes genital warts, is present in several skin layers beneath the wart itself. This is one reason it is so difficult to get rid of.
In 1988, FDA licensed alpha interferon to treat genital warts in patients who have not been helped by other therapies.

### Genital Wart Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy</th>
<th>Recurrence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>cryotherapy</td>
<td>63–88%</td>
<td>21–39%</td>
</tr>
<tr>
<td>interferon</td>
<td>44%</td>
<td>0% (recombinant alone)</td>
</tr>
<tr>
<td>interferon + podophyllin</td>
<td>61%</td>
<td>67%</td>
</tr>
<tr>
<td>laser vaporization</td>
<td>23–40%</td>
<td>not known</td>
</tr>
<tr>
<td>podofilox</td>
<td>45–88%</td>
<td>33–60%</td>
</tr>
<tr>
<td>podophyllin</td>
<td>32–79%</td>
<td>27–65%</td>
</tr>
<tr>
<td>surgical excision</td>
<td>93%</td>
<td>29%</td>
</tr>
<tr>
<td>trichloroacetic acid or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bichloroacetic acid</td>
<td>81%</td>
<td>36%</td>
</tr>
</tbody>
</table>

* up to 1 year, depending on the study

(Source: Centers for Disease Control and Prevention)

Warts that are extensive, scaly in appearance, or have been present for a long time are not likely to respond well to podophyllin. Patients who are pregnant, have diabetes, or are taking steroid drugs or have poor circulation are not good candidates for this treatment.

Condylux also is a plant extract, derived from mandrake or juniper plants. The patient can use it at home, after a doctor demonstrates how to apply it with a cotton-tipped stick. The patient applies the drug every 12 hours for three consecutive days, does not use it for four days, then repeats the three-day regimen, for a total of not more than four cycles. If it hasn’t worked by then, another treatment should be tried.

Most Condylux users experience a burning sensation, pain, inflammation, itching, or erosion of the affected area. Although Condylux has not been shown to harm fetuses, it is not advised for pregnant women because similar drugs are harmful.

Physicians sometimes use other topical treatments, such as trichloroacetic acid. This is a very caustic chemical that has not been tested very extensively on genital warts. Some physicians also use bichloroacetic acid or 5-fluorouracil, but FDA has not approved any of these for treating genital warts.

**Removal and Recurrence**

Visible genital warts can be physically removed using cold, heat, or excision by a scalpel or a laser. All of these techniques are uncomfortable, and the warts tend to recur because HPV is still present in surrounding cells.

Carbon dioxide laser vaporization and conventional surgical excision are best reserved for extensive warts, especially for patients who haven’t responded to other treatments, according to CDC’s 1993 Sexually Transmitted Disease Treatment Guidelines. These guidelines are not requirements, according to CDC medical epidemiologist Stuart Berman, M.D.

Stephen K. Tyring, M.D., Ph.D, associate professor at the University of Texas Medical Branch, and colleagues, including Brodell, writing in the June 1993 issue of The Female Patient, say that laser vaporization may require general anesthesia, is painful, and may require months to heal, sometimes leaving a whitish, scarred area. Surgical excision requires local anesthesia, and may produce scarring and lead to infection.

Cryotherapy is performed on less extensive lesions. This method uses liquid nitrogen or a device called a cryoprobe to freeze wart tissue, which then crumbles away. It is inexpensive, does not require an anesthetic, and is less likely to leave a scar than excision using a scalpel. However, most patients experience pain during and after the procedure. Cryotherapy with liquid nitrogen is especially well-suited for warts in hard-to-reach places, such as in the vagina.
Interferon

Interferon is a natural immune system biochemical. In treating genital warts, unlike other approaches, interferon attacks the responsible virus. One brand of alpha interferon used to treat genital warts, Alferon N, is obtained from white blood cells. The interferon is acid-treated and carefully screened for contaminants and viruses, says FDA's Finbloom. Another brand of alpha interferon licensed to treat genital warts, Intron A, is manufactured through genetic engineering.

Interferon was discovered in 1957, and its varied effects on immunity led scientists to hail it as a potential miracle cure for many conditions. However, it was difficult to obtain in sufficient amounts to test. With the advent of recombinant DNA technology in the 1970s, abundant, pure supplies of interferon became available to researchers. Not quite the magic elixir some expected, alpha interferon nevertheless is used today in the United States to treat hepatitis B and C, hairy cell leukemia, AIDS-associated Kaposi's sarcoma, and genital warts. Another form of interferon, Betaseran (or beta interferon), is approved to treat multiple sclerosis.

Treatment with interferon involves the doctor injecting the substance with a very small needle directly into each wart. Alferon N is injected twice a week, and Intron A three times a week. Treatment usually lasts eight weeks, with the lesions beginning to shrink by the fourth week. In one study, interferon was given along with podophyllin. The combination increased efficacy, but also raised recurrence rate.

About 30 percent of patients develop mild flu-like symptoms about two to four hours following treatment. For this reason, many doctors using interferon treat patients in the late afternoon, so that the patients feel well enough to go to work by the next morning. This side effect mimics the natural role of interferon in the body. The fever, aches and pains of a viral infection are actually caused by interferon and other immune system biochemicals readying the immune system to attack infecting virus, not by the bug itself.

Interferon therapy is expensive, usually costing from $1,100 to $1,200 for the entire treatment, counting office visits. CDC's 1993 treatment guidelines state, "Interferon therapy is not recommended because of its cost and its association with a high frequency of adverse side effects, and efficacy is no greater than that of other available therapies." Stone explains that the guidelines were based on analysis of published reports up until August 1992 of interferon's efficacy. "The bottom line was that the clearance rate [efficacy] and recurrence are not better than what you see with less invasive, less expensive therapies," she says.

Stone and others at CDC were particularly concerned about a woman who called them saying she had gone to a clinic in Atlanta and been asked to pay $2,000 up front for interferon treatment of a single wart. This was the first treatment the woman was offered. Yet Brodell reports that he has "patients whom I can't make better using traditional approaches, and I see 70 percent of them get better using interferon.

My patients typically have had two laser treatments, cryotherapy twice, and at home treatment with Condylox. I freeze the warts, use bichloroacetic acid, say magic words and bury a potato in the backyard, but it doesn't help," he says. Brodell finds the recurrence rate of genital warts using interferon to be about 25 percent.

Treatments Under Investigation

Elsewhere, other biological approaches are attempting to treat the underlying cause of genital warts. ISIS Pharmaceuticals in Carlsbad, Calif., is conducting clinical trials of a biologic called afovirsen that blocks HPV from using one of its key genes, disarming it from infecting human cells. Like interferon, afovirsen is injected into individual warts.

Researchers at Gilead Sciences in Foster City, Calif., are testing a topical drug called GS504 that blocks the virus from duplicating its genetic material. They are trying to see if this experimental drug, by entering nearby cells that are not yet infected, can prevent the virus from taking hold, according to company spokeswoman Lana Lauher. GS504 is currently being tested in people who are HIV positive or who have AIDS. Genital warts are especially severe in such people because their immune systems are suppressed. Therefore, if a treatment helps them, chances are good that it will also work on less severe cases.

Although genital warts are not life-threatening, they can cause great mental anguish. "Fortunately, a patient has many treatment options," says FDA's Finbloom.

Ricki Lewis is a geneticist and textbook author.
From dietary supplements, to food labels, to how to give medicines to kids—believe me, I’ve heard it all,” says Mary Margaret Richardson, FDA’s St. Louis-based public affairs specialist (PAS). “The broad questions on these and other subjects that were important to people 20 years ago—about their own health and safety, or the well-being of their families—are still important to them today.”

FDA’s PAS’s spend considerable time answering questions from the general public, as well as from the news media and just about anyone else wanting to know more about the products FDA regulates. Responding to queries on a wide variety of subjects—from female condoms to electromagnetic fields, from food labeling to mammography—the agency’s 44 PAS’s are walking encyclopedias.

They act as teachers, giving workshops and seminars to organizations about FDA’s work, and as representatives, appearing on broadcast media and assisting reporters in news story development. They also can be found helping the consumers across the country who call the myriad FDA district offices looking for information.

Though consumers have been asking the same kinds of health and safety questions since the 1960s and 1970s, FDA’s PAS’s are using more and different means to get answers. When Richardson started work as a PAS (then called a consumer affairs officer, or CAO) in 1971, she spent most of her time speaking one-on-one to health professionals, consumers, senior citizens, students, and other individuals.

“Today, I use the media—particularly TV and radio—a lot more of the time,” she says. “Through the media I can reach a wider audience with FDA’s messages.”

Those messages have changed, too. Consumers no longer take the government’s word on faith. They want all the information they can get—and then make up their own minds.

“We used to deliver the message: Because FDA is here, you’re safe. Today we say: Because FDA is here, you know more,” says Richardson, adding that no single agency can provide total safety to the public.

Lois Meyer, a PAS who recently retired after a 30-year FDA career in Buffalo, N.Y., thinks of her years with FDA as “both a teacher and a learner” experience.

“I never stopped having to learn new things about FDA programs, whether they involved medical devices or food labels,” she says. “In turn, I served as a teacher, a resource both for our publics and for FDAers in our field office who needed to know what the public was saying.”

FDA’s PAS’s have no standard training regimen or specific background as a requirement for the job. Some previously worked for the agency in another capacity, such as an investigator or compliance officer. Others are experienced in public relations. Though many perfect their trade by on-the-job experience, all bring to the job an enthusiasm.

by Betsy Adams and John Henkel

ILLUSTRATION BY DAVID CHEN
Mary Margaret Richardson (standing), public affairs specialist at FDA's St. Louis office, explains food labeling to a group of dietitian students at St. Louis University.

for FDA and exemplary public speaking and interpersonal skills.

In Meyer's case, a large part of her job was teaching people how to help themselves. For example, patients often called with questions about their medicines—questions that would best be answered by their own pharmacists.

"Sometimes the most helpful thing to do is make people aware of the tremendous resources already at their disposal," Meyer says. "If a consumer wants to know how much lead is in a piece of dinnerware, the people who sold you the product have a responsibility to help you get that information."

Established in 1952 as a cadre of consumer consultants, the original team of consumer affairs officers included only women—many of them homemakers who worked part time—with a home economics background. Today they include men, and their backgrounds are many and varied.

In 1972, Juan Tijerina of FDA's San Antonio resident post became the first man to join the group. Tijerina had been an FDA chemist for 10 years.

"I like to talk to people," he says. "I like to travel, and when the job for a bilingual CAO opened up, I jumped at the chance."

Tijerina remembers his first national meeting with the other CAOs.

"I could feel hundreds of eyes on me," he says, "not just those of my 55 women co-workers, but others at headquarters—wondering, I guess, why a man would want to join the group.

"I guess my motivation was much the same as the women's. I wanted to help people and help them understand the work we do," he says.

Recently Tijerina and two other Spanish-speaking PAS's—Al Gonzalez from San Juan and Estela Niella-Brown from Miami—went on a special assignment to Mexico City to teach food manufac-
How to Contact a Public Affairs Specialist

Consumers seeking information about FDA and the products it regulates can reach a public affairs specialist in their region by looking up the phone number of the FDA district office in the nearest large city's phone directory. One warning: FDA is not listed in the “F” section of federal government agency listings. Instead, it’s found in the “H’s” under “Health and Human Services” as an agency of that department.

Some FDA district offices have toll-free numbers, others require a long-distance call for those outside the district’s local dialing area. FDA “resident posts,” found in many smaller cities and listed in the phone book, also can forward questions to an appropriate PAS.

What kinds of questions can consumers ask? “Just about anything that has to do with FDA’s regulatory realm is fair game,” says Mary Margaret Richardson, PAS for FDA’s St. Louis office. “This includes drugs, biologics, medical devices, veterinary medicine, and food safety.”

Richardson says consumers sometimes call PAS’s to report faulty products or adverse reactions. These calls typically are subsequently referred to an FDA complaint coordinator. Sometimes, Richardson says, she gets calls concerning non-FDA responsibilities such as household devices or meat and poultry safety. She refers these to the Consumer Product Safety Commission, the U.S. Department of Agriculture, or other appropriate agency.

Because PAS’s are sometimes in the field and unavailable to take phone questions, Richardson suggests that callers “make good use of the phone mail system” PAS’s have. If they are seeking, say, a publication, they should give the publication name and number along with their address.

—J.H.

FDA’s public affairs specialists often use broadcast media to reach the public. Here, New York City-based PAS Herman Janiger describes an FDA program on a local news show aired over New York’s Channel One.
FDA’s 44 public affairs specialists respond to a variety of subjects, from female condoms to electromagnetic fields, from food labeling to mammography.

FDA public affairs specialist Barbara Miller explains agency programs to a group of New York City public school students and faculty.

health issues. And they have strong opinions on everything from dietary supplements to the pace of new product approvals. They keep me on my toes.”

Philadelphia PAS Theresa Holmes finds scientific and industry groups particularly challenging.
“Sometimes we have to shift gears in a hurry,” she says. “We may be translating science into lay terms for a consumer group one morning and then need to turn around and give a technical talk to scientists in the afternoon. Just call us ‘instant experts.’”

Although FDA’s PAS’s may vary widely in background and special skills, they all share a “can do” attitude. Orlando PAS Lynn Isaacs recalls, when she was stationed in Minneapolis some years ago, driving through snow drifts to Fargo, N.D., to conduct a consumer exchange meeting to solicit views on FDA issues.
“We drove up to City Hall, and there were several sound trucks and TV cameras,” she recalls. “We wondered what was going on, thinking maybe a rock group was in town.”

Turns out the cameras were there to cover the meeting.
“We were really big in Fargo in January!” she laughs.

New York City PAS Barbara Miller also had to brave the elements in 1993 to deliver a presentation to a group of high school students learning how to become government employees.
“I arrived in a raging downpour,” she says. “I was trying to be very serious and professional, but my clothes were soaked and my hair was dripping all over the floor. As my hair dried, it frizzed up, and my wet shoes squeaked throughout the talk.”

The group, she felt, was especially attentive during her presentation.
“I think the kids were fascinated to see someone who’d come out in such conditions just to speak with them,” she says.

Among retiree Lois Meyer’s fondest memories are those of the 1969 White House Conference on Food, Nutrition, and Health. “This led to the first, early attempts at nutrition labeling,” she recalls, “which ultimately led to today’s new food label.
“We learned early on in the process that you can’t develop regulations in a vacuum,” she says. “You have to find out what the public wants and needs.”

Overall, Meyer remembers her FDA career as one with a heavy workload but many satisfactions.
“As a PAS, I believe I had an effect on a great many lives by teaching consumers,” she says. “Since the agency can’t be everywhere at once, it’s important for consumers to be educated. That’s where I came in, and the other PAS’s. We’re all different—women and men, young and older, culturally diverse—and bring different interests and skills to the job, but we have the most important things in common: dedication to FDA and a lifelong interest in helping people.”

Betsy Adams is director of FDA’s press relations staff. John Henkel is a staff writer for FDA Consumer.
From the first glance at the newborn, the evidence is obvious—a tiny penis and a scrotum enclosing the testes.

No doubt about it: a male child.
But his gender wasn’t always so clear. For the first six weeks or so of gestation, this new baby boy appeared identical to a girl. He had embryonic gonadal cells that looked like they could quite normally develop into ovaries. He had tissue apparently capable of forming fallopian tubes, a uterus, and vagina.

At about 7 weeks of gestational age, testes began to form from cells that otherwise might have become ovaries. The hormone testosterone, produced by the testes beginning in the eighth week, initiated a cascade of actions and reactions causing a remarkable change in embryonic cells that had been on the road to becoming female organs and tissue. Testosterone promoted development of the penis and scrotum, formation of the structures involved in sperm production, and regression of tissue that, without testosterone, would have become fallopian tubes, uterus, and vagina. The result is announced at birth—“It’s a boy!”

Testosterone (one of the masculinizing hormones called androgens) continues to exert a spectrum of influences—sometimes quietly, sometimes furiously—throughout a lifetime. Little wonder that this powerful hormone has been approved by the Food and Drug Administration for the treatment of serious health problems caused by a deficiency or absence of naturally occurring androgens and that physicians and scientists here and abroad are trying to demonstrate other beneficial uses for the hormone.

**Fluctuating Hormones**

At birth, baby boys normally have testosterone blood levels close to those of adolescent and young adult males. But the level soon falls and remains relatively low until puberty, when testosterone and other hormone levels rise sharply. About 99 percent of American boys begin puberty between 9 and 14 years of age. The earliest sign of puberty is enlargement of the testes. Other changes—the appearance of pubic and other body hair, muscle and bone growth, deepening of the voice, and often acne—tell the world, to say nothing of the boy himself, that sexual maturation is well under way.

After puberty and into adulthood, a complex interaction among the testes, the adrenal glands (which also produce testosterone), and the pituitary and...
hypothalamic (located at the base of the brain) regulates levels of testosterone and other androgens. In adulthood, testosterone is thought to play a role, not only in sexual function, but in common adult male traits, such as loss of scalp hair and accumulation of abdominal fat—the all-too-familiar “spare tire.” Testosterone levels decline with advancing age, but some men retain essentially youthful testosterone levels well into their 70s and 80s.

The presence of presumably normal amounts of testosterone is believed to be associated with some potentially dangerous changes in men. For example, it probably stimulates excessive growth of the prostate, which can lead to urinary disorders and prostate cancer, the second most common cancer in American men. (See “Prostate Cancer: New Tests Create Treatment Dilemmas” in the December 1994 FDA Consumer.)

A number of problems, collectively called “hypogonadism,” result from failure of the testes to function normally because of genetic defect, illness, or injury. Unless an obvious abnormality is present at birth, delayed puberty may be the first indication that the testes are producing insufficient amounts of testosterone. If the malfunction occurs before the 12th week of gestation, male genitalia may not form fully or properly. When testosterone levels fall below normal after birth but before the normal onset of puberty, boys may begin puberty late or not at all, exhibit reduced growth of genitalia and body hair, retain a high-pitched voice, and show atypical bone growth and body proportions.

The consequences of hypogonadism beginning after puberty depend largely on the degree and duration of below-normal hormone levels. Typical effects are diminished libido, potency, sperm production, and overall strength. If the condition persists for a long time, the testes atrophy, fine wrinkles appear around the eyes and mouth, and body hair becomes sparse.

Testosterone Replacement
An estimated 150,000 to 200,000 boys and men in the United States are currently receiving testosterone to treat hypogonadism, although many more cases are thought to be undiagnosed and untreated. FDA has approved both oral and injectable testosterone products for use in hormone replacement therapy for boys and men who have hypogonadism. Testosterone is not readily absorbed and used by the body when taken by mouth. Most patients receive the drug by injection for their entire lives. An external patch that delivers the hormone through the skin of the scrotum has been approved by FDA for use in men 18 and older.

Carefully monitored testosterone replacement therapy, combined with other medical and psychological support, can help in cases of delayed puberty by inducing essentially normal growth and maturation. Mature men whose testosterone output is impaired because of illness, including chronic alcoholism, or injury also benefit from testosterone replacement and other medical treatment that can improve sexual and reproductive function.
An estimated 150,000 to 200,000 boys and men in the United States are currently receiving testosterone to treat hypogonadism.

A man opens a package containing a testosterone patch that he will place on the scrotum. Absorbed through the skin, the hormone treats hypogonadism.
Some scientists and physicians believe that testosterone therapy may help counter the effects of declining testosterone levels in older men—a normal consequence of aging. These investigators theorize that the decline of hormone levels is responsible for diminished sexual activity, bone and muscle loss, reduced vitality, diminished mental powers, and other physical and psychological deficits often seen in older men.

A number of studies in the United States, Europe, and Asia suggest that testosterone replacement therapy may counteract or retard these effects of aging. But they also confirm that using testosterone in this way can cause or aggravate undesirable growth, including cancer, of the prostate gland. Such treatment can also be very dangerous in patients with heart, liver or kidney disease. FDA has not approved the use of testosterone to treat conditions associated with aging. In this country, the only approved use for testosterone in males is treatment of hypogonadism. Androgenic hormonal drugs, including methyltestosterone, are approved for treating postmenopausal women with advanced inoperable breast cancer that has spread to skeletal bone.

Testosterone Replacement in Women?

There is a good deal of scientific uncertainty about the possible usefulness of testosterone replacement therapy in postmenopausal women, despite the claim by some authorities that it could have a role in women’s health. Although usually thought of as the “male” hormone, small amounts of testosterone are produced in the female body as well—chiefly by the ovaries and adrenal glands. Wide variations are common, but on average a woman’s blood has about 5 to 10 percent as much testosterone as a man’s. Among levels of the hormones estrogen and progesterone, women’s testosterone levels fluctuate during the menstrual cycle. They are highest at the time of ovulation. (Similarly, in men, the adrenal glands produce low levels of estrogens, the “female” hormones. See “Estrogen: Friend or Foe?” in the April 1995 issue of FDA Consumer.)

The role of testosterone and other androgens in female development and health is not well understood. Androgenic hormones, including testosterone, cause the growth of pubic and underarm hair in men and women and influence normal bone and muscle growth in both sexes. If androgens reach unusually high levels in an adolescent girl, they may produce effects ordinarily seen in pubescent males—excessive growth of facial and body hair, deepening of the voice, and worsening of acne.

In adult women, higher-than-normal testosterone levels have been associated with elevated blood pressure and increased risk of heart disease, diabetes, and uterine cancer, although these possible health effects have not been thoroughly studied.

There is some medical and scientific interest in using testosterone to treat certain symptoms in postmenopausal women. Some researchers speculate that among the problems for which testosterone may be beneficial are diminished sexual interest and response, loss of bone and muscle tissue, depression, and other physical and psychological changes—a spectrum of conditions not unlike that for which testosterone is being studied in older men. (The skin patch testosterone preparation, Testoderm, is not approved for use in women.)

Testosterone in the treatment of women has not been well studied in the United States, and data from other countries is sparse. Testosterone is used along with estrogen in some postmenopausal women receiving hormone replacement therapy at the Chelsea and Westminster Hospital in London. A similar treatment approach is followed in other European and Asian countries. FDA has not approved any applications for such uses in this country, however, and the vast majority of U.S. physicians do not prescribe it for this use as there is no substantial evidence that it provides any important health benefit or that its risks are acceptable in women.

Testosterone replacement therapy for men for conditions associated with normal aging is being studied, but is far from standard practice in the United States. But estrogen replacement therapy in women, though commonplace today, was once an unproven subject of research. Research has shown that estrogen can be used safely and effectively in the treatment of menopausal hot flashes and the prevention of postmenopausal osteoporosis in women. Whether science can establish a role for testosterone in the treatment of older men (and perhaps women as well) is a question that awaits further research.

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

- **Dietary supplement** nutrition labeling regulations will be enforced after Dec. 31, 1996, according to an FDA notice of intent. The next day, the agency will begin enforcing the 1994 Dietary Supplement Health and Education Act regulations. (FR Feb. 9)

- **Over-the-counter drug products** for preventing swimmer's ear or for drying water-clogged ears are not generally recognized as safe and effective, and are misbranded, according to an FDA final rule that takes effect Aug. 15. (FR Feb. 15)

- **A revised Vaccine Injury Table** was issued in a Health Resources and Services Administration final rule, effective March 10. The Vaccine Injury Compensation Program provides a no-fault compensation system for individuals who have been injured by specific vaccines. The table establishes presumptions about the causes of certain illnesses and conditions. Courts use the presumptions to award compensation. (FR Feb. 8)

- **Child choking incidents** caused by marbles, small balls, latex balloons, and toys or games containing these items must now be reported to the Consumer Product Safety Commission (CPSC) by manufacturers, distributors, retailers, or importers, according to a CPSC final rule that took effect March 29. In another rule, which takes effect Aug. 28, CPSC will impose labeling requirements for these items and ban certain small balls intended for use by children under 3. (FR Feb. 27)

- **Ophthalmic drug product review** is no longer conducted by the Anti-Infective Drugs Advisory Committee, according to an FDA final rule effective Feb. 17. Responsibility for this review was transferred to the Dermatologic and Ophthalmic Drugs Advisory Committee, formerly the Dermatologic Drugs Advisory Committee. (FR Feb. 17)

- **A pilot electronic docket** in FDA's Center for Devices and Radiological Health (CDRH) has been extended indefinitely. The docket, accessible by computer modem, contains CDRH policy speeches and statements, standard operating procedure guides, and other product evaluation and regulatory enforcement documents. The center no longer maintains printed copies of these documents. To access the electronic system, dial (1-800) 252-1366 or (301) 594-2741. For more information on the system, telephone the center's Division of Small Manufacturers Assistance at (1-800) 638-2041 or (301) 443-6597. (FR Feb. 7)

- **Two ecological risk assessment reports** are available from the Environmental Protection Agency. To order a free copy of "Ecological Risk Assessment Issue Papers" (EPA/630/R-94/009) and "Peer Review Workshop Report on Ecological Risk Assessment Issue Papers" (EPA/630/R-94/008), send your name, mailing address, and request for the documents by title and EPA number to: ORD Publications Office, CERI, U.S. Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268; telephone (513) 569-7562; facsimile (513) 569-7566. (FR Feb. 23)

- **Bicycle helmet injury control recommendations** for use by state and local agencies planning safety programs were published by the national Centers for Disease Control and Prevention. Each year, nearly 1,000 people die from bicycle crash injuries, and 550,000 people receive emergency room care. To order copies, which cost $1.50, request Morbidity and Mortality Weekly Report (MMWR), Vol. 44, RR-1, from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; telephone (202) 512-1800; facsimile (202) 512-2250. (MMWR Feb. 17)
Pesticide Applicator Sentenced to Five Years in Prison

by Kevin L. Ropp

A pesticide applicator who knowingly treated oats used by General Mills, Inc., with an unapproved pesticide chemical was sentenced to five years in prison, three years of supervised probation, and 200 hours of community service.

Y. George Roggy, owner of Fumicon, Inc., Edina, Minn., was sentenced Feb. 22, 1995, by Judge Michael Davis in the U.S. District Court for the District of Minnesota. In addition, on Aug. 31, 1994, Roggy surrendered his pesticide application license. The Minnesota Department of Agriculture had begun preparation for a revocation hearing.

On Nov. 15, a federal jury found Roggy guilty of fraudulently applying an unapproved pesticide to approximately 19 million bushels of oats. He was convicted of 11 counts of mail fraud, one count of felony food adulteration, and one count of misusing a pesticide.

General Mills unknowingly used some of the contaminated oats to manufacture approximately 160 million boxes of some of its most popular breakfast cereals, including Cheerios, Apple Cinnamon Cheerios, Honey Nut Cheerios, Multi Grain Cheerios, and Lucky Charms.

FDA’s Kansas City district became aware of the contamination May 24, 1994, after routine tests by the agency of oat samples collected from two Iowa feed mills. Analysis showed the oats contained chlorpyrifos-ethyl, a pesticide approved for pre-harvest use on raw agricultural commodities, but not for any use on oats. FDA investigators traced the source of the oats to a General Mills plant in Fridley, Minn.

On June 6, Minneapolis district investigator Frank Sedzielarz collected oat samples from General Mills’ Superior, Wis., grain elevator. FDA analysis of these oats confirmed they contained chlorpyrifos-ethyl at levels of up to 2.65 parts per million (ppm). Since the pesticide is not approved for use on oats, its presence caused the General Mills oats to be adulterated, according to former Minneapolis compliance officer Jeffrey Spykerman.

On June 8, Sedzielarz interviewed Roggy, who told the investigator he applied Reldan 4E (chlorpyrifos-methyl) but never used Dursban 4E, the chlorpyrifos-ethyl. “One of the two containers he pointed out to Sedzielarz was labeled as Reldan, which is an approved product. Sedzielarz collected a sample of the chemical, sent it to the laboratory, and found it was Dursban, the chlorpyrifos-ethyl,” Spykerman said.

On June 10, General Mills stopped distributing oats stored in its grain elevators and finished products in its inventory after being notified by FDA that the oats and oat products contained an unapproved pesticide.

Two days later, General Mills confronted Roggy, and he admitted that he had used Dursban instead of Reldan because it was cheaper and that he had
Investigators' Reports (continued)

been applying Dursban to the oats for more than a year. He said he knew what he had done was wrong and that he was surprised FDA caught the switch, Spykerman said. General Mills officials informed FDA of Roggy’s statement.

On June 16, after obtaining a search warrant, agents from FDA’s Office of Criminal Investigations, the U.S. Department of Agriculture’s Office of Inspector General, and the Environmental Protection Agency seized receipts for the purchase of Dursban from Roggy’s home and two semi-trailers he used to store chemicals.

According to court documents, Roggy applied the unapproved Dursban and billed General Mills for applying Reldan. He submitted invoices to General Mills totaling approximately $166,120, which falsely claimed that he had used Reldan. Roggy saved about $85,000 by using the unapproved pesticide.

General Mills destroyed 55 million boxes of cereal it had in inventory and suffered losses of more than $140 million. In a March 24 Federal Register final rule, EPA granted General Mills’ request allowing the firm to sell its stored oats for animal feed.

General Mills has strengthened its quality control testing of grains and finished products and said it will contract with a national pesticide firm to handle its pesticide-application program.

Kevin L. Ropp is a member of FDA’s public affairs staff.

Decayed Tuna Destroyed

Rotten, smelly tuna that caused illness in four family members was buried by U.S. marshals in a Florida landfill.

The decomposed frozen tuna, destroyed last fall, was the last of a shipment of more than 12 metric tons seized between March and July 1994. There were three seizures in Seattle, where the original shipment was held, and one in Pensacola, Fla.

In December 1993, the Okaloosa County Health Department in Fort Walton Beach, Fla., notified FDA of four cases of scombroid poisoning, a food-borne disease caused by histamine-like toxins that result from bacterial decomposition in certain fish. Histamine is a chemical found in all organic matter and released in allergic reactions.

The victims became flushed and developed nausea and diarrhea within one hour of eating the fish at a Fort Walton Beach restaurant. They were treated in a hospital emergency room and released after two hours. The restaurant immediately stopped serving the fish.

FDA analysis of the fish showed above-normal levels of histamine extracts.

The agency traced the decomposed fish to ATL Cold Storage Co. in Pensacola, Fla., where it was stored under the account of Seven Seas Seafood Inc. of Alahambra, Calif. That supply, about 1.5 metric tons worth an estimated $6,500, also was rotten.

An investigator in FDA’s Los Angeles district office visited Seven Seas and determined that the spoiled tuna had been part of a lot shipped to Seattle, where the bulk of it was still being stored at City Ice and Cold Storage Co.

FDA tests found that the tuna in Seattle also was decomposed. At FDA’s request, Washington state officials embargoed the lot.

Several companies owned the fish at that point: Arctic Alaska Fisheries Inc., Seattle; Daerim America, Maywood, N.J.; and Source International Food Products Inc., La Connor, Wash., which had sold some fish to companies in Massachusetts and California and left some in storage.

Notified by FDA, Seven Seas Seafood and Source International voluntarily recalled the tuna they had distributed to several dealers. Arctic Alaska Fisheries did not conduct a recall.

U.S. marshals seized and destroyed the tuna belonging to Arctic Alaska, Source International, and Daerim America.

No other illnesses were reported.

—Paula Kurtzweil

Firm Gets New Management After History of Deficiencies

A medical device distributor recalled its thoracic catheters three times in two years after FDA investigations found many deficiencies—including failure to report potentially serious problems. The catheters are used to drain chest wounds.

Problems uncovered by investigations from May 1992 to May 1994 led the distributor, Deknatel, Inc., of Fall River, Mass., to institute changes under a new management team. FDA is monitoring the changes.
Deknatel bought the catheters from the manufacturer, Mallinckrodt Anesthesiology of Argyle, N.Y., and then packaged them in pouches and sterilized them for distribution.

According to Gary Hagan, an investigator with FDA's Boston district office, the catheter is inserted through an incision and pulled by its blue tip outside the body. The catheter is then cut to the desired length, and the end is placed in a receptacle for collecting the draining fluids. The tip was soft, Hagan says, to prevent trauma to the patient during the insertion procedure. It also served as a seal for the end of the catheter outside the body. This seal—meant to replace clamping—prevented fluid spill while the drainage system was set up.

“What was happening,” Hagan says, “was that the tip would come off when pulled, and the fluids would go all over the patient, the bed, and the staff caring for the patient.”

FDA knows of no deaths or serious injuries caused by the faulty devices.

On Jan. 31, 1992, Deknatel reported to FDA a complaint it got the previous November from a hospital in Canada. A tip had dislodged, and a nurse reattached it with adhesive. The firm classified the complaint as potentially serious. On April 21, Deknatel notified FDA it was sending safety alert letters concerning size 32S catheters to its consignees, and did so the next day. FDA considered the alert a recall.

On May 6, during a three-week inspection of Deknatel, Hagan and colleague Domenic Veneziano discovered five unreported complaints from 1991 and another five from 1992. The complaints involved size 16S catheters as well as size 32S. Deknatel had classified the complaints either as category “B” (malfunction or failure to perform as specified) or “C” (appearance defects).

“Under Deknatel’s classification,” Hagan says, “these complaints weren’t expected to result in death or serious injury and, therefore, weren’t reportable to FDA.” Yet an internal company memo dated Jan. 2, 1992, stated, “If the blue tip were to come off outside the operating room, in recovery or in the ICU, this would be of significant clinical danger to the patient and blood exposure to the nursing staff.”

Other documents showed that after Deknatel received two complaints in March 1991, the firm’s quality control division had asked for specifications for the minimum force that would remove a tip. However, Hagan says, “The firm didn’t begin testing the tips’ bond strength until January 1992.”

The investigators also found three complaints about another product—blood vessel punch blades mislabeled as a smaller size. Deknatel classified the complaints as “B” and didn’t report them. Yet an internal memo on the blades stated that the mislabeled product “would likely cause an alteration in normal practices.”

This type of blade is used with a precision punch to create an opening in blood vessels that are to be connected, as in types of arterial bypass surgeries. According to FDA cardiologist Jeffrey Jones, M.D., a larger-than-expected punch hole could pose risks such as bleeding.

Deknatel repackaged and resterilized the blades in stock, but because it didn’t change the outer packaging codes to match those on the reprocessed inner packets, the lot numbers didn’t agree. Also, the firm didn’t recall the mislabeled blades that were already distributed.

Deknatel’s records also showed the firm had sold silk sutures without adequate airing after gas sterilization.

Among other deficiencies, Deknatel:
• did not report reportable complaints
• did not gather adequate information to properly evaluate complaints
• did not properly test its catheter tips after receiving the first complaint
• did not identify the cause of the mixed-up blade sizes
• did not control its packaging operations
• did not have an adequate remedial plan.

Confronted with the investigators’ findings, Deknatel voluntarily recalled the suspect 16S catheters on May 14, 1992, and the mislabeled reprocessed blades on June 1.

On June 18, Michael Sinkevich, of FDA’s Buffalo district office, inspected Mallinckrodt Anesthesiology. He determined the tips fell off because the operator used insufficient solvent in assembling the devices. The firm retrained the operator.

To obtain information on the recalled blades, Hagan and investigator Alfred Levitt inspected Deknatel in August 1992. Problems continued, and Deknatel promised to correct them.

Following a recall of mislabeled sutures and another inspection, FDA sent Deknatel a warning letter dated Jan. 14, 1993, admonishing the firm for not reporting complaints and for not correcting its manufacturing problems. Three more recalls, more inspections, and more promises of corrections ensued.

On March 22, 1993, more than 300 recalled catheters were destroyed in an incinerator in Lawrence, Mass.

On Sept. 20, 1993, following a complaint about a tip falling off a size 28S catheter, Deknatel recalled five lots of this size. Like the other recalled catheters, the devices had been improperly manufactured by the Mallinckrodt operator before the person’s retraining. On April 29, 1994, 84 were incinerated.

In April and May 1994, Hagan and investigators Sherry Nissen and Paul Geraci inspected Deknatel again and still found problems. They also found, however, that the firm had constructed a new management team.

“When Deknatel officials came in for
a meeting shortly after the inspection," Hagan says, "they convinced us they were making the needed changes. It will take time, but there's accountability now. We saw much improvement."

FDA closed out the last of the recalls on July 1, 1994.
—Dixie Farley

**Wisconsin Foot Doctor Jailed For Selling Drug Samples**

A Janesville, Wis., podiatrist was jailed early this year for Medicare fraud and for illegally selling prescription drug samples, a violation of the Prescription Drug Marketing Act (PDMA).

Alfred J. Galluzzo, D.P.M., reported to prison Jan. 3, 1995, following sentencing Nov. 30, 1994, to 11 months in jail for each of two counts, to be served concurrently, followed by three years of supervised probation. Galluzzo was also fined $20,000, ordered to pay $1,734 a month for confinement costs, and ordered to pay $180.90 a month for supervision costs.

In addition, the Wisconsin Department of Regulation and Licensing revoked Galluzzo's state medical license.

Galluzzo pleaded guilty Oct. 6, 1994, to one count of filing a false Medicare claim and one count of unlawful sale of the prescription drug sample Vicodin (hydrocodone bitartrate with acetaminophen), a controlled substance.

FDA's Madison, Wis., resident post and Minneapolis district office first learned of the possible PDMA violation in November 1992. A month earlier, John Isely, a special agent with the U.S. Department of Health and Human Services' Office of Inspector General was investigating Galluzzo for possible Medicare fraud. Isely searched the garbage from the Galluzzo Foot Clinic.

"In going through the trash, Isely found a lot of shucked packaging, some of which clearly stated that these were prescription drug samples, including Vicodin and Lorcet Plus," said Chuck Cote, resident-in-charge of FDA's Madison post. "He picked up on the fact that this was an odd situation and contacted me—it snowballed from there."

On Dec. 12, Cote interviewed a former employee of Galluzzo, who said one reason she left his employment was that he was selling physician samples, which he got free from at least two drug companies. She also said she helped remove these samples from their packaging and knew Galluzzo was selling them to his patients. Interviews with several other former employees confirmed this information.

"We were fortunate," Cote said. "Under PDMA, manufacturers and distributors are required to keep track of the distribution of samples. In addition, because these are schedule III drugs, controlled by the Drug Enforcement Administration, the manufacturers keep even tighter reign over them."

Cote contacted the two drug manufacturers, who provided information correlating the lot codes of the samples they gave Galluzzo with the codes from the empty packaging found in the clinic's garbage.

In addition, the manufacturers confirmed that Galluzzo had been requesting and receiving physician samples from February 1991 through Dec. 8, 1992. Based on the manufacturers' information, FDA estimated that Galluzzo repacked and sold over 2,000 sample tablets worth several thousand dollars.

On Feb. 11, 1993, after obtaining a search warrant, Cote and Isely together searched Galluzzo's clinic, seizing records and files to support both charges.

Cote said that from conversations with current and former employees, he determined that "Galluzzo didn't buy any of the brand-name drugs so, obviously, the brand-name drugs he was selling to patients were the samples he had received and repackaged."

In addition, based on evidence collected by Cote and Isely, the U.S. Department of Occupational Safety and Health on March 18, 1993, fined Galluzzo $65,000 for improper handling and disposal of medical wastes, including needles and other sharp instruments, and improperly discarding tubes containing blood.

On Sept. 20, 1994, the U.S. attorney charged Galluzzo with the two felony counts.

—Kevin L. Ropp

**Summaries of Court Actions will not appear in this issue of FDA Consumer, but will return in the June issue.**
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