

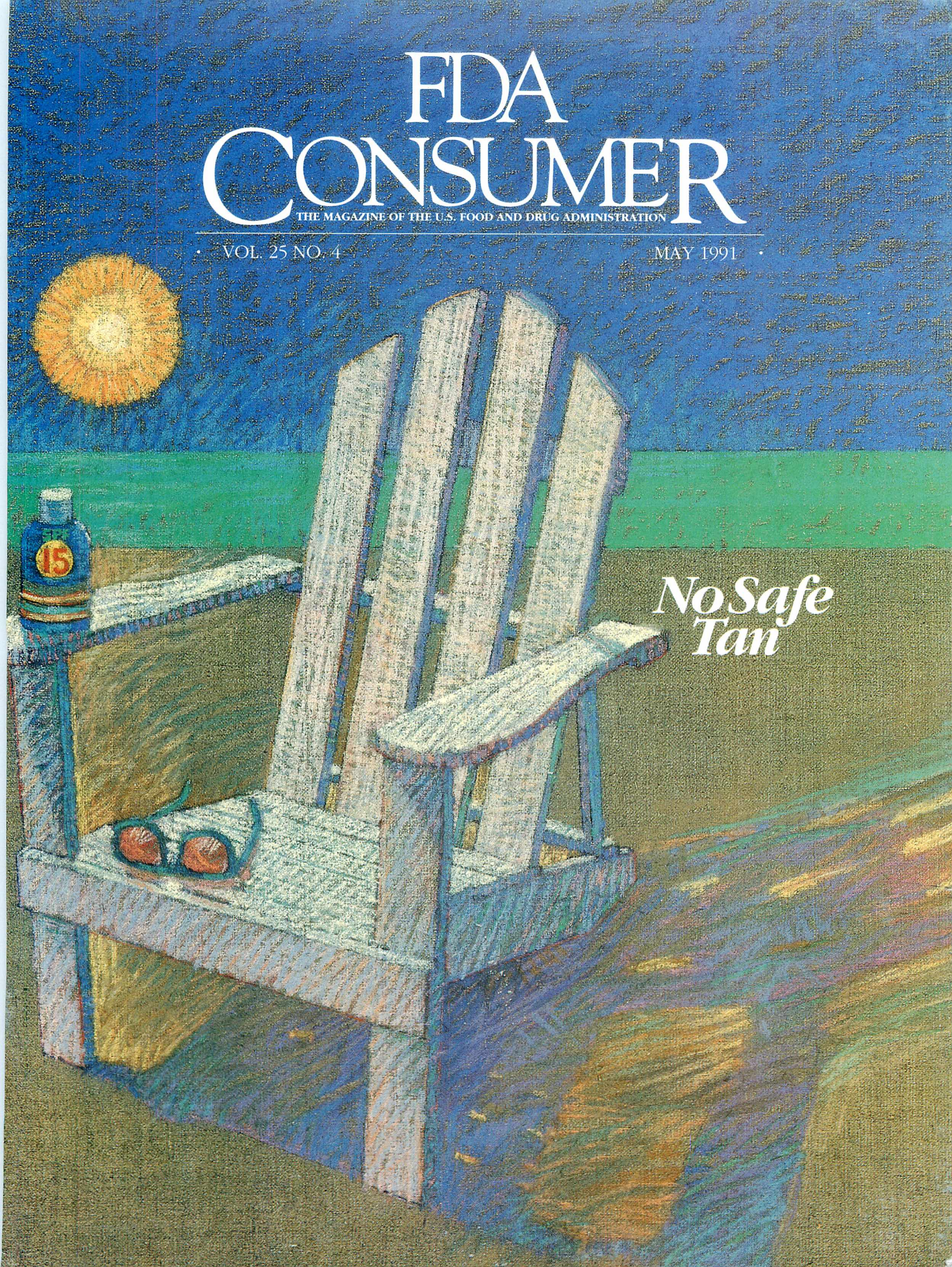
FDA CONSUMER

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

VOL. 25 NO. 4

MAY 1991

*No Safe
Tan*





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FDA CONSUMER

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Norplant: Birth Control at Arm's Reach 8
A hormone implanted under the skin of a woman's upper arm is the latest family planning option. Though highly effective, its side effects mean that it's not for everyone.

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Laser surgery and other therapies have simplified treating ailing gallbladders. And though gallbladder removal appears to be on the decline, if it's necessary you're fine without this organ.

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People have enjoyed herbal teas for centuries. But they've been the subject of controversy since their introduction into the mainstream U.S. marketplace 20 years ago.

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Inside Front Cover Photo: *Foxglove, though pleasing to view in the garden, can cause erratic heartbeats if consumed in brewed tea. For more on possible problems with some herbal teas, see page 30.*



New Drug Fights Infection In Cancer Patients

G-CSF, a genetically engineered drug that can stimulate production of infection-fighting white blood cells in cancer patients undergoing chemotherapy, was approved by FDA last Feb. 21.

White blood cell counts can become dangerously low in some cancer patients undergoing chemotherapy, leaving them vulnerable to life-threatening infections. The type of chemotherapy for which G-CSF is indicated—myelosuppressive chemotherapy—destroys certain immune cells in addition to tumor cells. It is used to treat about 225,000 cancer patients each year. Patients will be given G-CSF daily for 10 to 14 days, beginning one to two days after their chemotherapy treatment. The drug does not affect the underlying malignancy, and there is no evidence that it enhances survival.

"G-CSF is a pioneer therapeutic product," said FDA Commissioner David Kessler, M.D. "Other biotechnological therapeutics have held high promise, but proved to be useful to only a small number of patients. G-CSF will be useful in treating a large number of cancer patients."

In clinical trials, no serious side effects from G-CSF were reported. The most common adverse reaction, mild to moderate bone pain, could be controlled in most patients with acetaminophen.

G-CSF is one of a group of proteins called colony stimulating factors, produced naturally by the body to regulate production of different types of blood cells. They are found only in tiny amounts in human tissue, but can now be mass-produced using gene-splicing techniques.

Amgen, Inc., of Thousand Oaks, Calif., manufactures G-CSF using recombinant DNA technology. The drug is produced in a special laboratory strain of *Escherichia coli* bacteria that have been genetically altered by adding a gene for human granulocyte colony stimulating factor.

Amgen will market the drug in the United States under the trade name Neupogen.

(For more information on colony stimulating factors, see "Genetic Engineering Yields Disease-Fighting Hormones" in the July–August 1990 *FDA Consumer*.)

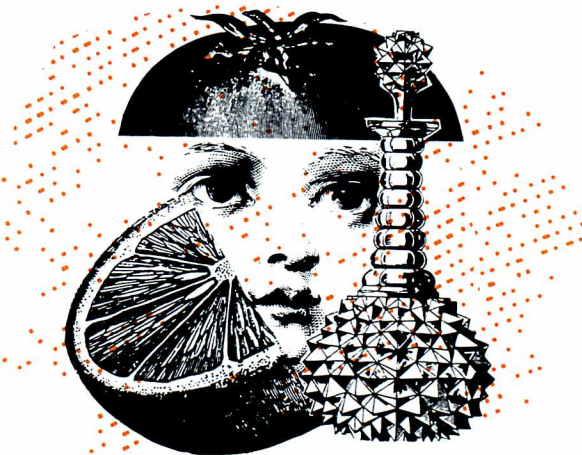
Crystal May Leach Lead into Food

Leaded crystal decanters may be beautiful, but they also may pose a serious health threat, a recent study suggests.

Researchers from FDA and Columbia University's College of Physicians and Surgeons found that when alcoholic and other beverages are stored in crystal decanters, the decanters release lead into the liquid. As a result, FDA is advising people not to use crystal decanters or other crystal ware to store beverages or foods.

FDA warns that infants and children are particularly vulnerable and may experience adverse health effects even from low levels of lead exposure. The agency advises the following:

- Don't store foods or beverages, especially alcoholic beverages and other products with a high acid content (fruit juice, tomato sauce, vinegar, wine, etc.), in crystal glassware.
- Don't feed infants and children from crystal baby bottles or glasses.



- Pregnant women should not use crystal glassware.
- Decrease the frequency of use of crystal wine glasses, particularly by women of childbearing age.

FDA tested 60 samples of crystal ware from 17 different countries for leachable lead content. In the experiments, FDA scientists used in the glassware an acetic acid solution similar in acidity to household vinegar. Results showed that over a 24-hour period, amounts of lead released into the solution ranged from non-detectable levels to 7.2 parts per million. One experiment shows that when acidic juices or warmed infant formula were poured into crystal baby bottles, lead levels in the beverages rose. FDA and the crystal ware industry are performing additional studies on the release of lead by crystal glassware.

FDA presently has no maximum allowable level for lead leached from crystal ware. But experts recognize that lead is hazardous to health. Because lead accumulates in the body, limiting exposure to it is essential.

Advice About Theophylline

In response to public concern about media reports of severe adverse reactions among asthma patients taking the drug theophylline, FDA gives the following advice to such patients and their families:

- A patient taking theophylline should contact a physician *immediately* upon developing any of the following symptoms of theophylline overdosage: sustained high fever, nausea, vomiting, excessive irritability, insomnia, or tremor.
- Parents of children under a year old should know that this age group is particularly vulnerable to theophylline toxicity.
- Blood levels of theophylline should be monitored when therapy begins, when dose levels are changed, and when other medications are added or other medical conditions develop that might affect levels of the drug.
- Patients should not exceed their prescribed dose of theophylline unless so directed by a physician.

Theophylline, a drug closely related chemically to caffeine, has been marketed in the United States for more than 50 years. It is an effective treatment for asthma, and serious adverse reactions are rare in patients whose blood levels of the drug fall within the accepted therapeutic range.

FDA says that such reactions can be avoided through proper patient monitoring and dose selection. Over the last 20 years, the agency has advised the medical community on the safe use of theophylline through advisory committee meetings, labeling guidelines, and *Drug Bulletin* articles for health professionals.

(For more on childhood asthma and theophylline, see "More Than Snuffles: Childhood Asthma" and "Keeping Time to Circadian Rhythms," both in the July-August 1990 issue of *FDA Consumer*.)

Anabolic Steroids Controlled Substances

Anabolic steroids were placed in Schedule III of the Controlled Substances Act on Feb. 27, 1991. Drugs in this category include those that may have some legitimate therapeutic uses, but also carry a potential for physical or psychological dependence. Only persons registered with the Drug Enforcement Administration and approved to distribute Schedule III drugs will be able to dispense anabolic steroids.

Anabolic steroids are synthetic versions of the male sex hormone testosterone. According to DEA administrator Robert C. Bonner, athletes, body builders, and adolescents use the drugs in the hopes of enhancing their

athletic performance or physical appearance. However, anabolic steroids can cause serious health problems, including stunted growth; liver, heart and kidney disease; personality changes; sterility; and even death. Despite the serious health threat from these compounds, athletes continue to use them. (See the Updates section in the December 1990 *FDA Consumer*.)

Placement of anabolic steroids in Schedule III is required by the Anabolic Steroids Control Act of 1990, passed by Congress in response to increased use of the drugs. According to a 1989 General Accounting Office report, the illegal trade in anabolic steroids is a \$300-million to \$400-million-a-year industry.

Anyone with a current supply of anabolic steroids must either surrender it to DEA authorities or transfer it to an approved dispenser. The maximum penalty for a first offense of trafficking or illegal dispensing of anabolic steroids is five years in prison and a \$250,000 fine, according to DEA's Bonner.

Treatment for Hepatitis C

A genetically engineered product originally licensed in 1986 to treat hairy cell leukemia was OK'd by FDA Feb. 25, 1991, to treat non-A, non-B hepatitis, also called hepatitis C.

The product, alpha interferon, is the first effective treatment against this form of hepatitis, which affects an estimated 150,000 Americans each year. Hepatitis C is usually caused by contact with infected blood and blood-derived products. It can progress to chronic hepatitis, marked by fatigue and weight loss, and possibly to cirrhosis, liver failure, and death in some patients.

Alpha interferon is a genetically engineered copy of a protein found naturally in low levels in the human body. In multi-center studies, 166 patients were given injections of the biological for six months. About half of the group treated with high doses showed improvement and, of those, half maintained the beneficial response for up to six months after stopping treatment.

Adverse reactions reported with the use of alpha interferon for hepatitis include headaches, fever, and other mild, flu-like symptoms. The side effects appear to lessen during continued therapy.

Besides hairy cell leukemia and hepatitis C, alpha interferon is licensed for treatment of AIDS-related Kaposi's sarcoma and genital warts. Schering-Plough Corporation of Kenilworth, N.J., which markets a version of the product under the trade name Intron-A, received approval for the product's use for hepatitis.

For more information on hepatitis, see "Hepatitis B:

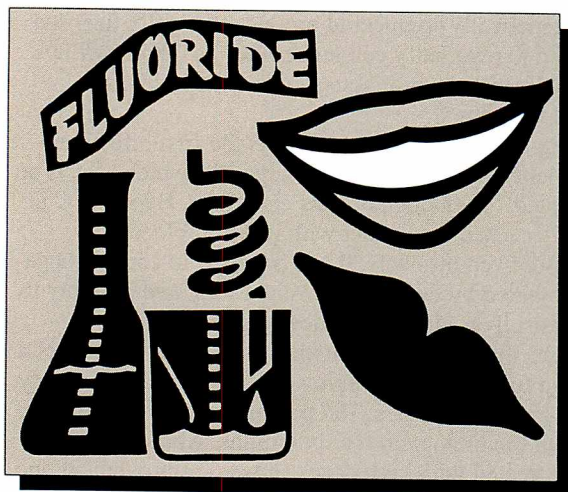
Available Vaccine Safe but Underused" in the May 1990 *FDA Consumer*.

Government Assesses Fluoride

Fluoridated drinking water does not pose a detectable risk of causing cancer in humans, but some people may be getting more of the mineral than they need, a year-long government investigation concluded recently.

Scientists from FDA's National Center for Toxicological Research participated in the study, which was led by the U.S. Public Health Service and included researchers from more than a dozen federal research agencies.

The benefits of fluoridated water outweigh any risks, the study held. More than half of all Americans drink water with fluoride added by local governments for its benefits in preventing tooth decay. Although other factors may contribute, the average child today has about



one-third as many cavities as children had before fluoridation in the mid-1940s.

In releasing the report, Assistant Secretary of Health James O. Mason said that in areas of the United States where the water naturally contains more than recommended amounts, children do not need additional fluoride. The extra fluoride might cause dental fluorosis, a discoloration of the teeth.

To prevent dental fluorosis, the report recommended that doctors prescribe fluoride dietary supplements only when the home water supply is deficient in fluoride. It also recommended that parents instruct children to rinse

carefully after brushing and not to swallow fluoride toothpaste.

Public Health officials requested the study after preliminary research at the National Toxicology Program found that fluoride causes cancer in rats. When 130 male rats drank water containing high levels of fluoride (more than 100 parts per million) over a lifetime, four of them developed osteosarcoma, a rare bone cancer.

But drinking water for humans contains much lower levels of fluoride. EPA recommends no more than 2 parts per million in drinking water and allows no more than 4 parts per million.

The Public Health Service reviewed the results of more than 50 epidemiological studies over the last 40 years and found no evidence linking the low levels of fluoride in drinking water with bone cancer in humans. There are about 750 new cases of osteosarcoma among Americans each year, and although the number seems to have increased, the study found no association with the disease and the onset of fluoridation.

The report also found no evidence to link fluoridation with Down syndrome, gastrointestinal problems, or diseases of the genitourinary and respiratory systems.

The study found conflicting epidemiological evidence on the role of fluoride in strengthening or weakening bones. While European doctors use fluoride to treat osteoporosis, several studies conflict over whether there are clear benefits in doing so. A 1989 FDA report concluded that fluoride was not effective in reducing osteoporosis fractures.

Trichinosis Outbreaks

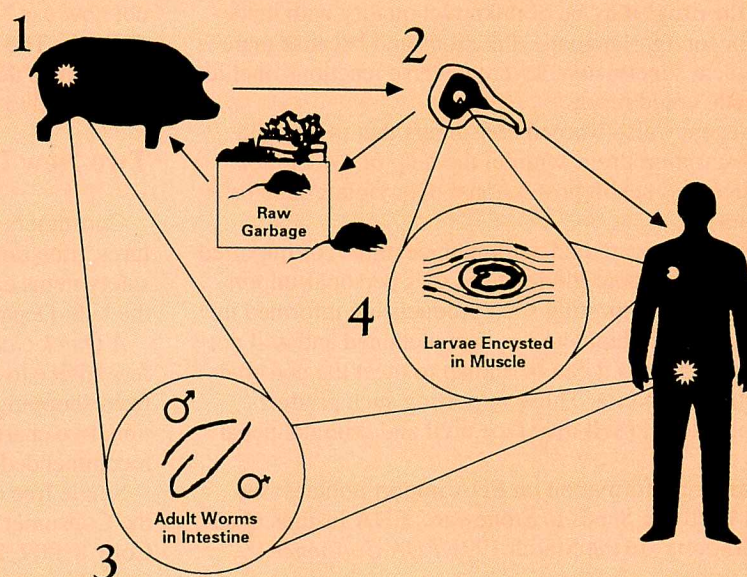
Two outbreaks in 1990 of trichinosis (infection with *Trichinella spiralis* worm larvae) due to eating undercooked infested pork point up the need for consumers to continue guarding against this preventable, sometimes fatal illness. The U.S. Centers for Disease Control in Atlanta warned in its Feb. 1, 1991, *Morbidity and Mortality Weekly Report* that the risk is particularly high when people routinely eat undercooked pork, as is the practice among Southeast Asian immigrants.

Of the 250 people at a wedding of Southeast Asians last July in Des Moines, Iowa, 90 developed trichinosis—the fourth outbreak since 1975 among the 900,000 immigrants in the United States. The illnesses were linked to pork sausage that was uncooked, which is the customary way to serve that food in Southeast Asian

Life Cycle of *Trichinella Spiralis*

1. Wild or domestic food animal ingests larvae by eating infested farm rats or infested flesh of another animal.
2. Humans eat contaminated meat from the slaughtered infested animal.
3. Larvae grow to adult worms in host's intestine, where they release new larvae able to pass through the intestinal wall.
4. Traveling in the bloodstream, larvae that reach muscle tissue survive by enclosing themselves in protective sacs.

Source: *Morbidity and Mortality Weekly Report*, Feb. 1, 1991.



culture. To kill *T. spiralis* larvae, a person must cook pork until it is well done, to 66 degrees Celsius (150 degrees Fahrenheit).

Last November and December, four Virginia counties reported another outbreak of 15 sausage-related cases. One victim denied eating undercooked sausage but was a meat handler in the plant that processed the implicated meat. CDC received reports of 15 additional cases occurring singly in 1990. No deaths were reported.

Trichinosis symptoms are fever, muscle soreness, and upper eyelid swelling. Lab tests show increased eosinophils (white blood cells).

CDC noted that the proportion of cases from commercial pork has declined since 1975, probably because of laws prohibiting feeding raw garbage to pigs, increased use of home freezers, and the practice of thoroughly cooking pork. On the other hand, there has been an increase in the relative importance of another source: wild game—including bear, boar and walrus.

Warning on Importing Drugs

Importing drugs from abroad except under certain circumstances is illegal, FDA warns, and potentially harmful. The agency is especially concerned with foreign versions of U.S.-approved drugs imported from abroad.

There has recently been some confusion over FDA's policy on drug importation, with some claims that people can save money on drugs and doctor bills by "legally" importing foreign versions of drugs that have been approved in the United States. This is not true.

FDA does allow individuals to import drugs that are not approved in the United States if they meet specific conditions. The drugs must be for personal use only, in amounts to be used by one person for up to three months. This personal use policy does not extend to U.S.-approved drugs.

This policy allows people with serious conditions, such as AIDS, to import through the mail personal-use

quantities of unapproved drugs that they feel might be helpful in treating their conditions. The policy is also intended to allow people to import through their personal baggage small quantities of medicines with which they may have been treated while traveling abroad.

The drugs cannot pose any "unreasonable or significant" safety risks, cannot be commercialized, and must be used for a serious condition for which no satisfactory treatment is available in this country.

According to FDA to otherwise import foreign drugs could pose an "unreasonable" risk to public health. Because the drugs may be of unknown quality with inadequate or foreign-language directions and because there is no medical supervision, severe adverse reactions, including death, could result.

The agency also warned consumers that to buy and use prescription drugs without the help of a doctor or other licensed health professional may violate state or local laws.

FDA will recommend automatic detention of imported products that appear to violate FDA's personal-import policy. People importing such products are informed in writing that the shipment has been detained and will not be released unless it can be shown to meet the personal-use entrance criteria. Those importing such products with the intent to sell may face civil and criminal penalties.

(For more information on FDA import policies, see "From Psyllium Seeds to Stoneware: FDA Insures Quality of Imports" in the March 1991 *FDA Consumer*.)

When Is Food Fresh?

Because of confusion over the meaning of the term "fresh," FDA is reevaluating the use of the word on processed foods and has asked the food industry to refrain from using the term until new standards are developed.

Although the agency first addressed the issue 50 years ago, new technologies and new products have stretched the boundaries of what constitutes "fresh."

Beginning in the 1940s, FDA agreed to allow the term "fresh frozen" on produce that had indeed been frozen while still fresh. At the same time, it barred use of the designation on butter that had been churned previously and held in cold storage awaiting shipment.

FDA's current policy states that the term "fresh" should not be applied to foods that have been subjected to any form of heat or chemical processing. The agency recently issued letters to two firms because they misused the term on their products, one a pasta sauce and the other orange juice made from concentrate.

As outlined in a *Federal Register* notice published

Feb. 12, 1991, the agency is currently surveying and reviewing food labels now on the market to identify issues that must be addressed in defining the term "fresh." The *Federal Register* notice also discussed a petition FDA received from the California tomato packers requesting the agency to issue a regulation that would, among other things, prohibit use of the term "fresh" on finished tomato products containing previously processed tomato ingredients.

Until a final regulation is issued, FDA asks manufacturers, packers, and others who label foods and who do not now use "fresh" on the label to refrain from using the term. The agency may examine all freshness claims. Companies that can prove their products are fresh will be allowed to use the designation.

Two New USDA Food Safety Pubs

Consumers concerned about proper cooking temperatures, time limits on cold storage of food, and other food safety items can find tips from a new publication from the U.S. Department of Agriculture.

A *Quick Consumer Guide to Safe Food Handling* offers advice to consumers on all aspects of food handling, from shopping to cooking to serving leftovers. In addition, two charts list proper cooking temperatures and recommended cold-storage time limits.

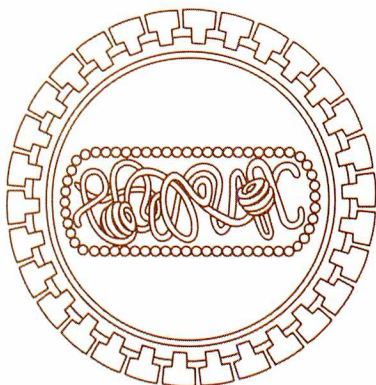
Single free copies of the guide may be ordered from the Consumer Information Center, Box 574-X, Pueblo, Colo. 81009. Bulk copies are not available, but black-and-white reproductions can be provided for reprinting. The reproductions are available from USDA, FSIS Publications Office, Room 1165-South Building, Washington, D.C. 20250.

A second publication from USDA, *Preventing Foodborne Illness*, is designed for professionals interested in food safety and provides more in-depth information about food-borne illnesses than the consumer's guide. It also offers guidelines on handling foods needing special care, such as ground meats, ham, poultry stuffing, and eggs.

Single free copies of *Preventing Foodborne Illness* may be ordered by calling USDA's Public Awareness Office at (202) 447-9351 or writing to USDA, FSIS Publications Office, Room 1165-South Building, Washington, D.C. 20250. Bulk copies are not available to the general public.

(See also "The Unwelcome Dinner Guest: Preventing Food-Borne Illness" in the January-February 1991 *FDA Consumer*.)

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



Committee Reaffirms Early Retrovir Treatment

After reviewing new information on previous drug studies, the Antiviral Drug Products Advisory Committee last February reaffirmed to FDA that Retrovir (zidovudine, commonly called AZT) is useful treatment at early stages of HIV infection. The expert panel recommended additional analyses to resolve apparent differences in study results that have emerged since the drug was approved.

Preliminary results of a Veterans Administration (VA) study generally confirmed that early Retrovir use helped delay the onset of AIDS, but further data analysis indicated the drug's effects might vary significantly among ethnic groups. For instance, the African-American and Hispanic patients given Retrovir later may have fared better than those given the drug earlier. The committee recommended that other studies be evaluated to see whether the differences were unique to the VA study. It recommended that studies be conducted to identify possible contributing factors, such as the high percentage of intravenous drug use among the participants and different overall medical care standards.

The committee also reviewed recent data from two clinical trials conducted by the National Institute of Allergy and Infectious Diseases. These trials were the basis for FDA's approval of Retrovir in March 1990 to treat patients at less advanced stages of HIV infection. Follow-up data continue to show that such patients benefit from the drug.

Research on Treating HIV in Minorities

A program to encourage research on therapies to treat HIV infection in minorities has been begun by the National Institute of Allergy and Infectious Diseases (NIAID).

NIAID awarded three grants last January to help develop AIDS clinical trials units with a research focus on minorities. The awards, totaling \$2,406,784, were given to researchers at Howard University in Washington, D.C., the University of Hawaii, and the University of Puerto Rico. These three institutions were not involved in NIAID's AIDS Clinical Trials Group, a nationwide network of AIDS clinical trials units that evaluate experimental therapies.

Anthony S. Fauci, M.D., director of NIAID, commented that "HIV infection and AIDS in minorities pose special—and urgent—challenges for NIAID in our efforts to combat this disease. HIV infection is steadily increasing in minorities, yet minority racial and ethnic groups and minority-focused concerns have been underrepresented in AIDS clinical research. We believe these grants will help address these important issues."

As of January 1991, minorities (primarily African Americans and Hispanics) constituted about 44 percent of the 157,525 cases of AIDS reported in the United States since the epidemic began in 1981. African Americans make up 12 percent of the total U.S. population, yet they account for 28 percent of the AIDS cases. Hispanics make up less than 8 percent of the total U.S. population, yet they account for approximately 15.5 percent of AIDS cases.

Study Compares DDI, DDC

The first national clinical trial comparing the effectiveness of two experimental AIDS therapies will be conducted at 18 sites in 14 cities as part of the Community Programs for Clinical Research on AIDS (CPCRA) under the

auspices of the National Institute of Allergy and Infectious Diseases (NIAID).

Dideoxyinosine (DDI) and dideoxycytidine (DDC) will be given to about 400 HIV-infected persons as part of the program to increase participation in AIDS clinical trials by HIV-infected women, minorities, and drug users, who have sometimes been underrepresented in such studies. Study participants must either be intolerant of or have failed treatment with Retrovir (zidovudine, commonly called AZT), the only drug approved to treat AIDS.

FDA granted DDI treatment IND (investigational new drug) status in September 1989, allowing distribution to AIDS patients who cannot take Retrovir. In addition, DDI has "open label" study status for severely ill AIDS or advanced HIV-infected patients whose disease has progressed despite Retrovir treatment. In "open label" studies, all patients receive experimental drugs (no placebos are given), and there are usually no strict limits on the number of people enrolled.

DDC is also available through open-label safety studies to patients with AIDS or advanced HIV-infection who have failed to respond to or who are intolerant of Retrovir or DDI.

Participants in the CPRA study will be randomly assigned DDI or DDC and followed regularly for two years. Patient records will be coded to protect confidentiality. The study will compare disease progression, effect on T4 cell counts, and frequency and severity of side effects.

Both DDI, manufactured by Bristol Myers Squibb Co., and DDC, manufactured by Hoffmann-La Roche, showed activity against the AIDS virus in phase I clinical studies. However, at higher doses, some patients experienced painful nerve damage called peripheral neuropathy to hands and feet. In addition, some patients taking DDI have developed inflammation of the pancreas.


More information about this and other trials is available by calling 1-800-TRI-ALS-A weekdays from 9 a.m. to 7 p.m. Eastern time.



NORPLANT

Birth Control at Arm's Reach

by Marian Segal



The newest birth control option for women is literally at arm's reach. The Norplant contraceptive, approved by the Food and Drug Administration last December and marketed since February, is implanted just under the skin of the inner arm, right above the elbow. Developed by the Population Council of New York, this birth control alternative is distinctly different from methods previously available.

New Form, Old Content

Norplant consists of a familiar ingredient in a new package. Six silicone rubber capsules about the size of matchsticks contain a synthetic progestin hormone long used in birth control pills. The flexible tubes are inserted in a fan-like arrangement and can be felt but not easily seen.

Once in place, they steadily release a low dose of hormone into the bloodstream. Effective within 24 hours after insertion, Norplant can continue to prevent pregnancy for up to five years.

The hormone usually inhibits ovulation so that eggs are not produced regularly, and causes the mucus of the cervix to thicken, making it more difficult for sperm to reach the egg. Other ways that Norplant may provide contraceptive effects have been proposed but not proven.

Experimental Attitude

Jennifer Collier, a 28-year-old New York law student, entered a study of Norplant at the Robert Wood Johnson Institute in New Brunswick, N.J., in the spring of 1984 and is now on her second implant, inserted last June.

"It sounded like a really neat invention, so I decided to try it," says Collier. She had been dissatisfied with the weight gain and irritability she experienced using oral contraceptives. With Norplant, she says, she isn't troubled with either of those side effects. Collier describes the implant as visible, "but not terribly obvious. No one has noticed it unless they were looking for it, probably partly because of where it's inserted."

Each Norplant capsule is 2.4 millimeters (about one-tenth of an inch) in diameter and 34 millimeters (just under one-and-a-half inches) long, and holds 36 milligrams of powdered crystals of the progestin levonorgestrel. The tubes are made of Silastic, a silicone material long used in surgical implants such as heart valves and hip joints.

The hormone seeps through the permeable tubes into the bloodstream, initially at a rate of about 85 micrograms a day. The amount declines gradually to about 50 micrograms by nine months, 35 by 18 months, and about 30 micrograms at the end of five years. In comparison, birth control pills that contain levonorgestrel provide about 50 to 150 micrograms of the progestin a day, plus estrogen. (The only progestin-only contraceptive avail-

able in the United States contains 75 micrograms of norgestrel, a progestin similar to levonorgestrel.)

When the hormone supply dwindles, usually in about five years, a new implant can be inserted if desired. On the other hand, if a woman wishes to become pregnant earlier, she can have the implants removed at any time, and fertility is restored very soon. Blood levels of the progestin are undetectable within 5 to 14 days.

Population Council Project

Norplant has been marketed in other countries for several years. According to the Population Council, more than half a million women in 46 countries have used the implant since it was first approved in Finland—where it is manufactured—in 1983. It now has regulatory approval in 17 other countries as well, including Sweden, Indonesia, the Dominican Republic, Thailand, China, Peru, and the United States. Norplant's U.S. distributor is the Philadelphia-based pharmaceutical firm Wyeth-Ayerst Laboratories.

"The first implants were tested in 1968," says Population Council vice president Wayne Bardin, M.D., "and then the council began to develop and test implants that released a whole variety of progestins. By 1974, we came up with what is now the Norplant implant, using levonorgestrel. The first clinical trial of that was begun in 1975."

FDA approval of the implant was based on the results of clinical studies involving 2,400 women in the United States, Finland, Sweden, Denmark, Jamaica, Brazil, Chile, and the Dominican Republic.

In the studies, the contraceptive's ef-

Effectiveness Rates of Contraceptive Methods

(Shown are the number of pregnancies for every 100 women during the first year of use)

Method	Lowest Expected	Typical
Male sterilization	0.1	0.15
Norplant	0.2	0.2
Female sterilization	0.2	0.4
Oral contraceptives		3
Combined	0.1	*
Progestin only	0.5	*
IUD	<1	3
Condom without spermicide	2	12
Cervical cap	6	18
Diaphragm with spermicide cream or jelly	6	18
Vaginal sponge		
women who haven't borne children	6	18
women who have borne children	9	28
Spermicides alone (foams, creams, jellies, and vaginal suppositories)	3	21
Periodic abstinence (all methods)	1-9	20
No contraception (planned pregnancy)	85	85

* = not available

(Source: Adapted from Table 1 in *Studies in Family Planning*, 1990, by J. Trussell et al.)

fectiveness approached that of sterilization in the first year. (See chart above.)

Pregnancy rates were slightly higher in heavier women, increasing after the third year of use in those who weighed more than 69 kilograms (153 pounds). Nevertheless, the protection is still quite good. For example, among 100 women of all weights using the implant for five years, it is expected that four would become pregnant during that time. By contrast, of 100 women using the pill for the same time, at least 15 might be expected to become pregnant.

Norplant's effectiveness does not depend on patient compliance—a feature shared by only one other type of reversible contraceptive—the intrauterine device, or IUD. This particularly appeals to Collier for the convenience it affords. “Unlike the pill, you don't have to remember to take it every day, and, unlike the diaphragm, there's no problem with spontaneity,” she says.

Because Norplant is not a barrier contraceptive, however, it offers no protection against sexually transmitted diseases such as AIDS, herpes, chlamydia, and gonorrhea. For optimum protection from both disease and pregnancy, couples may choose to use both Norplant and a condom.

The Drawbacks

As with virtually any drug or medical device, Norplant isn't entirely trouble-free. Side effects that women have reported with the implant during the first year include irregular menstrual bleeding, headache, nervousness, depression, nausea, dizziness, skin rash, acne, change of appetite, breast tenderness, weight gain, enlargement of the ovaries, and excessive growth of body or facial hair.

Some Norplant users have also reported breast discharge, vaginal discharge, inflammation of the cervix, abdominal discomfort, and muscle and skeletal pain. These effects, however, cannot be linked to use of the implant because the complaints are common among the general population and could stem from many other causes. There is no known biological reason to link the complaints specifically to use of the contraceptive.

By far, the most common side effect is menstrual cycle irregularity. “To give the percentage of women with menstrual irregularities is complex,” says Bardin, “because it changes with time.” He says that over a five-year period of use, about 45 percent of women will have irregular periods and another 45 percent will have

normal periods. The remaining 10 percent will have long periods of time—three to four months—with no bleeding. “That's an average,” says Bardin. “Basically what happens is you have more women with irregular periods in the first year and that tends to diminish with continuing use.”

The bleeding irregularities result from the continuous hormone release. “With the oral contraceptive pills, estrogen and progestin are taken for three weeks and withdrawn for one week, causing regular bleeding,” explains Lisa Rarick, M.D., a medical officer in FDA's division of endocrine and metabolism drug products. “Norplant, on the other hand,” says Rarick, “provides no cyclic withdrawal, and thus each individual creates her own bleeding pattern.”

In the multi-center trials, more women had increases in their hemoglobin concentrations than decreases, indicating that they lost less menstrual blood when using Norplant. (Hemoglobin is the oxygen-carrying pigment of red blood cells that gives them their red color and serves to transport oxygen to tissues.) Bardin says that this is because, on average, even if the number of bleeding days increases in the first year of use, the total amount of blood lost may be less than

would be lost without hormonal contraception.

He says that most women who use Norplant don't perceive bleeding as a problem. "To illustrate," he says, "if you say, 'What is the biggest complaint that women have about Norplant,' it's bleeding irregularities. But if you ask all women if bleeding irregularities bother them, something like 60 percent say 'no.'"

Collier says she has spotting and a lighter flow with Norplant. "Sometimes, I have no discernible cycle at all," she says, but maintains that "although of course I'd rather have regular periods, the effects are not that bad."

Nevertheless, the major reason women give for discontinuing Norplant is bleeding problems, accounting for about 9 percent of those who stop in the first year, according to FDA's Rarick. Another 5 percent stop for other medical reasons, from headaches to dizziness, and perhaps another 5 percent stop for other reasons, including to have a baby. She estimates that about 60 to 65 percent of women continue with the implant longer than two years.

Not for Everyone

More serious complications are possible as well, and Norplant is not recommended for everyone. As with oral contraceptives, women with acute liver disease or liver tumors—whether malignant or benign—unexplained vaginal bleeding, breast cancer, or blood clots in the legs, lungs or eyes should not use the implant.

Norplant contains only progestin, whereas most oral contraceptives contain both progestin and estrogen. Some side effects of the pill, such as eye disorders and increased risk of cardiovascular problems among women who smoke, are believed to be related to the estrogen component. Nevertheless, FDA advises physicians to "consider the possible increased risks associated with oral contraceptives, including elevated blood pressure, thromboembolic disorders [blood clots obstructing blood vessels], and other vascular problems that might occur with use of the contraceptive implant."

Bardin suggests that Norplant will be most attractive to women who:

- wish to use highly effective low-dose hormone contraception
- want long-term contraception after completing their family, but don't want sterilization

***E**ffective within 24 hours after insertion, Norplant can continue to prevent pregnancy for up to five years.*

- want to delay childbearing for an extended period of time
- cannot use estrogens
- are unhappy with other forms of contraception.

On the flip side, Bardin expects the implant to be less popular among women who:

- are happy with their present form of contraception
- cannot or do not want to pay the up-front cost of Norplant
- will not tolerate irregular menstrual bleeding if it should occur
- do not want to use a method that requires a visit to a health-care professional to discontinue. ("Some women feel that puts them at the mercy of the clinic and they want to be able to stop it any time they want," says Bardin. "That's why they like pills and barrier methods—it's under their control," he says.)

Surgical Insertion

Successful use of the Norplant system depends on careful insertion of the capsules. Wyeth-Ayerst markets the implant as a kit with detailed instructions for insertion and removal, and, through the Association of Reproductive Health Professionals, offers physician training programs as well.

The firm describes the insertion as a minor, outpatient surgical procedure requiring only 10 to 15 minutes. The area is numbed with a local anesthetic, and a small incision, less than an eighth of an inch long, is made. Using a special instrument called a trocar, the physician places the six capsules just under the skin. The incision is then covered with protective gauze and a small adhesive

bandage. Stitches are not required.

When the anesthetic wears off, there may be some tenderness or itching, and perhaps some temporary discoloration, bruising and swelling. Infection at the site of insertion has also been reported.

It takes a bit longer to remove the implant than to insert it—usually from 15 to 20 minutes, according to the distributor. As with insertion, a small incision is made under a local anesthetic. Then the physician removes the capsules and, again, the incision is covered with an adhesive bandage. Sometimes, some capsules may be more difficult to remove than others. When this happens, the woman may have to return a second time, after the area has healed, for removal of the remaining capsules.

The reason for suggesting the second visit, Bardin says, is to let the physician know that "if you have trouble removing, don't cut a big hole in the woman's arm and go fishing around looking for it [the capsule]." If the anesthetic has caused the area to puff up, for example, it may be difficult to feel the implant. "Wait until the next week or whenever she can come in again," says Bardin, "and you'll be able to see it and take it out with minimal trauma."

If desired, a new set of implants can be inserted at the same time the old set is removed, either in the same arm and through the same incision, or in the other arm.

The price to the medical professional for a single Norplant system, which includes all the necessary apparatus for insertion and removal as well as the set of six capsules, has been set at \$350. Fees for insertion and related costs, such as counseling and removal, vary, depending on the physician.

Collier says that this will probably be the last Norplant she'll have, at least for a while, as she plans to get pregnant eventually. She's not sure if she would come back to the implant later. "Hormone therapy and the risks associated with it—more with the pill and estrogen than with Norplant—concern me," she says. "I'll just have to see what else might be available when that time comes." For now, Collier is pleased with Norplant and would recommend it to any woman, "especially," she says, "if they're going to be on hormone therapy anyway." ■

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



Liver

Gall
bladder

Pancreas

Spleen

Stomach

Small
intestine

Large
intestine

The Gallbladder

An Organ You Can Live Without

by Ricki Lewis, Ph.D.

Even though she was about 15 pounds overweight, the woman indulged in her favorite fatty foods with gusto, consuming fried chicken, french fries, and topping it off with a hot fudge sundae. By 3 a.m., she regretted her actions, awakening with indigestion and a sharp, stabbing pain in the upper right quarter of her abdomen. The pain continued for hours, spreading to her shoulders, slowly ebbing away by the next afternoon.

Since the symptoms had abated and no one else in the family became ill, the woman forgot her experience—until a few weeks later. This time, the seeming culprit was a pizza binge, another fatty meal. The unrelenting, severe abdominal pain returned. Finally, the woman went to her doctor, who immediately suspected a gallbladder problem.

Although this woman is a composite of several gallstone patients, her experiences are fairly typical. She was not one of the 10 percent of patients whose gallstones contain calcium, which makes them visible on a standard x-ray. So she was given a tablet containing a radio-paque dye the night before undergoing a special x-ray called an oral cholecystogram. The dye outlined her gallbladder and individual stones within it. Had the dye not shown up at all, it would have meant that her gallbladder was packed full with stones. An ultrasound scan confirmed the presence of stones.

The diagnosis: acute cholecystitis. The tube leading from her gallbladder to her small intestine was blocked by a cholesterol stone. Pressure was building in her gallbladder, alerting the immune system to send in the white blood cells and biochemicals of an inflammatory response.

Although she was in intense pain, the woman would soon be helped by recent developments that make treating a diseased gallbladder easier than ever.

The Gallbladder

The gallbladder is a small, muscular, pear-shaped sac nestled in a depression

on the right underside of the liver. It holds about a quarter of a cup of a yellowish-green, pasty material called bile. Bile contains water, bile salts and acids, pigments, cholesterol, phospholipids (a type of fat molecule), and electrolytes (electrically charged fluids). Bile tastes bitter, and this is why the word “bile” has come to denote bitterness. Bile breaks up, or emulsifies, large globs of fat into smaller globs in the small intestine, a first step in fat digestion.

The gallbladder is a storage stop between the liver and the small intestine. It fills with viscous bile, thickening it, until a hormone released after eating signals the gallbladder to squirt out its colorful contents.

A healthy gallbladder keeps bile moving in several ways. The inner lining, called the mucosa, secretes hydrogen ions into the gallbladder contents. This maintains an acidic environment, necessary to keep calcium from precipitating (coming out of solution as solid particles). As food is digested, water and electrolytes pour into the area, continually diluting and washing out the bile. Finally, bile salts latch onto cholesterol molecules, keeping them in solution.

Stone Formation

Should any of these biological balances backfire, the sludge-like gallbladder contents can crystallize. A stone forms when a speck of calcium becomes coated with either cholesterol or the pigment bilirubin. Bilirubin comes from the blood's oxygen-carrying molecule, hemoglobin. The brownish-black color of pigment stones is due to bilirubin, much as a vibrantly hued bruise appears as blood spreads beneath the skin.

While pigment stones are small, dark, and relatively rare, cholesterol stones are crystalline and waxy, can grow quite large, and may accumulate in the hundreds. Many stones are mixed, with pigment on the inside, wrapped in a cholesterol coat.

About half of people with gallbladder

stones do not even know that they have them. Painless stones probably float freely in the gallbladder. Pain results when a stone is small enough to pass through and lodge in either the cystic duct leading from the gallbladder, or farther along in the common bile duct, which is shared by the gallbladder and the liver and leads to the small intestine. In fact, one large stone trapped in the gallbladder is not as likely to cause pain as are several small stones that can escape.

The type and severity of symptoms depend upon where stones lodge. A stone stuck in the lower common bile duct results in jaundice (yellowing of the skin and whites of the eyes, due to bilirubin accumulation) and may cause pancreatitis, because a conduit from the pancreas joins the common bile duct. The pancreas' digestive enzymes, which normally go to the small intestine, become trapped in this essential gland, destroying it.

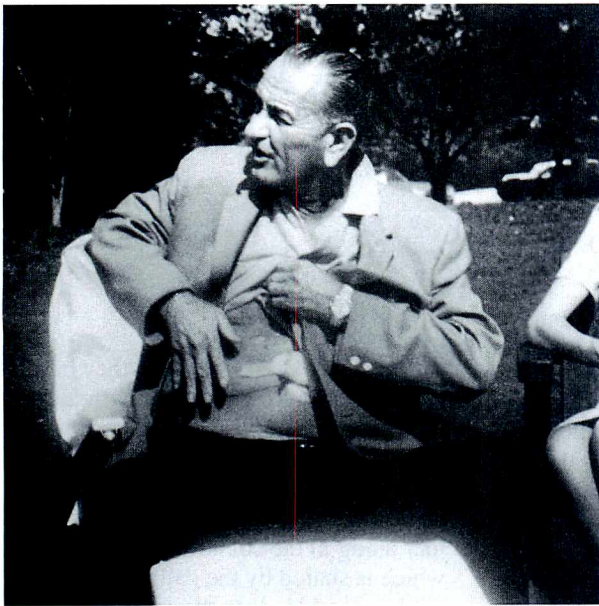
A stone trapped in the neck of the gallbladder causes acute cholecystitis. A milder condition is chronic recurrent acute cholecystitis, characterized by intermittent pain of shorter duration and less intensity.

In the most severe scenario, pressure builds so much that the gallbladder bursts, sending bile into the abdominal cavity. Pus accumulates, bacteria move in, and the infected bile may lead to peritonitis, a severe infection of the abdominal cavity. But this is very rare because a gallbladder is usually removed before disease can progress this far.

Who Gets Gallstones?

Although gallstones are a very common medical problem, we know very little about why some people develop them and some do not. We do know that women are twice as likely to have gallbladder problems as men.

Women may owe their higher risk of gallbladder disease to hormones. The female hormone estrogen is known to in-



In a photo taken during his presidency, Lyndon B. Johnson shows the scar from his gallbladder operation performed by traditional surgery. The scar extends several inches horizontally on the right side between his waist and his navel. (Photo by Dennis Brock, Black Star Inc.)

crease the rate of lipid (fat) synthesis, use and excretion, while at the same time calming gallbladder movements that would mix up the contents. Pregnancy raises risk by altering the chemical composition of bile to favor stone formation and decreasing the contractability of the gallbladder. Birth control pills containing estrogen increase the cholesterol content of bile, and seem to heighten the risk of gallbladder disease in women under 29 who have taken them for less than 5 years.

Studies indicate that gallstones are more prevalent in some populations than others, but it is difficult to tell whether this is due to heredity or environmental factors. For example, gallstones are common in the United States (with 20 million sufferers) and Great Britain (with 100,000 affected) and have the highest incidence in Sweden, where 44 percent of the population is affected. Yet gallstones are very rare in Africa and Asia.

But does prevalent gallbladder disease reflect a particular diet, or genetic similarity among the people? It's hard to say.

The fact that the rate of gallbladder disease is high in cultures with high-fat, low-fiber diets and low in cultures with high-fiber, low-fat diets suggests a nutritional influence. In addition, people who move from the high-fiber, low-fat areas to high-fat, low-fiber areas soon develop more gallbladder disease. For example, East Asians moving to the United States and adopting our fattier diet show a sixfold increase in gallbladder problems within a single generation.

On the other hand, certain population groups, most notably Native Americans,

among the Navajos of the southwestern states, the Chippewas of northern Minnesota, the Micmacs of Nova Scotia, Alaskan tribes, and especially the Araucanian Indians of Chile. Another genetic link is the association of pigment gallstones with sickle cell disease, an inherited anemia most common in blacks.

The Role of Diet

Since the gallbladder is part of the digestive system, it seems logical that its health would depend, at least in part, on what one eats. Establishing a dietary cause of gallbladder disease is difficult.

Still, some clinical studies track interesting trends. A group of Boston researchers led by K. Malcolm MacLure, Sc.D., of the Harvard School of Public Health, and Walter C. Willett, M.D., of Harvard Medical School, followed 88,837 women between the ages of 34 and 59 who had filled out a detailed dietary questionnaire in 1980. By 1984, 433 had had their gallbladders removed, and 179 had stones not yet treated. What, if anything, did these women have or do that the others didn't? Weight.

"Overall, we observed a roughly linear relation between relative weight and the risk of gallstones," write the researchers in the Aug. 31, 1989, issue of the *New England Journal of Medicine*. They warn that even moderate overweight can raise the risk, estimating that the very obese face a sixfold higher risk, and the slightly overweight a 1.7-fold increase in risk.

Another recent study suggests that what one eats is also important. A team led by Harris Pastides, Ph.D., of the University of Massachusetts School of Pub-

lic Health in Amherst, compared the diets of 84 female and 16 male gallbladder patients admitted consecutively to a hospital in Athens, Greece, to accident victims without gallbladder problems. They conclude in the July 1990 *Archives of Internal Medicine*, "Our findings suggest that there is a rather strong association between frequent consumption of starchy food items such as breads, pasta, rice, and potatoes with risk of gallbladder disease in women. Furthermore, a modest protective effect was observed among women reporting relatively high consumption of vegetables of all kinds." They recommend that overweight women with starchy diets try to include more vegetables.

But the diet-gallbladder link, if indeed there is one, is far from clear. Consider a class action suit being filed against a popular dietary plan. "Last spring, according to newspaper reports, 19 people filed suit against NutriSystem for developing gallbladder disease after the diet," says Carol Heppe, a consumer safety officer at the Food and Drug Administration. But would they have become ill anyway? There is no ready answer.

For women, common risk factors for developing the disease include age, weight, and number of children. Among obese women between 20 and 30 years of age, the risk is six times greater than that for women of normal weight. By age 60, almost one-third of obese women can expect to develop gallbladder disease.

Drug Treatment

Drug treatment to dissolve gallstones began about 20 years ago, when researchers found that a deficiency of bile salts enabled cholesterol to crystallize out of solution and form stones. Today, drugs are typically given for small stones or if a person cannot tolerate surgery.

The two approved cholesterol gallstone dissolution drugs are the natural bile constituents chenodeoxycholic acid (Chenix) and its chemical non-identical twin ursodeoxycholic acid (Actigall).

"These drugs can change the cholesterol saturation in the gallbladder and permit cholesterol in the stone to go into solution, so that it dissolves," says Stephen Fredd, M.D., director of FDA's division of gastrointestinal and coagulation drug products at FDA. "Ursodeoxycholic acid is less likely to be toxic to the liver, but is more expensive."

But the drugs have major drawbacks. "In 50 percent of patients, stones recur within five years of drug treatment," ex-

plains Fredd. "A common side effect of these drugs is diarrhea. The drugs work slowly and must be taken daily for a long time and, even then, are not always effective. About 12 percent of patients improve after six months, and up to 50 percent show improvement by a year. The cost of drug treatment is about \$1,200 a year.

A new investigational drug is methyl-tert-butyl-ether. It works fast on cholesterol stones, dissolving them in 24 to 48 hours, but administering the drug is an invasive procedure.

"It is not taken orally," explains Fredd. "It is put in the gallbladder by a catheter through the liver to the gallbladder. This is not minor stuff, but in expert hands, it can be done safely. But it has dangerous propensities. It is an ether, and can put you to sleep. It can irritate the intestines."

Another new drug is mono-octanoin (Moctanin), which is approved only to treat stones lodged in the common bile duct. This sometimes happens after the gallbladder is removed and small stones migrate into the duct.

Shock Wave Lithotripsy

Shock wave lithotripsy, a noninvasive procedure that FDA approved for treating kidney stones in 1985, seemed to hold great promise for treating gallstones as well. (To treat kidney stones, the torso of the anesthetized but conscious patient is immobilized and lowered into a large tub of water, where x-rays are used to locate the stone and position the patient properly. In a procedure lasting one to two hours, the kidney stones are then crushed, without harming bone or soft tissue, by repeated shock waves from a generator at the bottom of the tub.)

"At the outset we thought, gee, it'll be great for gallstones, too. But gallstones turned out to be a whole different animal," says FDA's Mark Kramer, chief of the office of device evaluation's gastroenterology/urology branch I.

Not only are gallbladder stones chemically different from kidney stones, but kidney stones are easier to pass once shattered because urine forms in the kidney and collects in the bladder all the time. In contrast, the gallbladder squirts only intermittently, and may not contract and expand enough in patients who form stones for the stones to be passed. As a result, gallstone dissolution drugs usually must be taken along with the lithotripsy treatment. Based on the clinical data available, lithotripsy for gallstones may only work for 10 to 15 percent of suffer-



The gallbladder is lifted out through a half-inch incision during laser surgery. Traditional gallbladder surgery requires a 5- to 8-inch incision.

(Photo courtesy of New Jersey Laser Institute)

ers, Kramer says, and it is not yet known which types of patients would benefit more from it than from drugs or surgery.

Surgery

Cholecystectomy—gallbladder removal—is the most common elective abdominal operation in western nations. Before the procedure was perfected a century ago, the cholecystostomies performed only removed the stones—which came back. Researchers then realized they had to remove the stones plus their pouch, the gallbladder. In a classical cholecystectomy, the surgeon removes the gallbladder through a 5- to 8-inch incision. The duct from the liver is then attached directly to the small intestine. Afterwards, a steady trickle of less concentrated bile is sent to the small intestine. In most cases, life returns to normal.

Cholecystectomy costs from \$6,000 to \$10,000, and requires a five- to seven-day hospital stay. The patient needs about a month to fully recover. Considering the invasiveness of the procedure, and that symptoms are often intermittent or even nonexistent, it is not surprising that the operation is declining in popularity. In 1975, 600,000 cholecystectomies were performed in the United States; by 1989, the number had dropped to 475,000.

A new surgical procedure, laparoscopic laser cholecystectomy (LLC, popularly known as "keyhole laser surgery"), is an alternative to conventional cholecystectomy. It is fast, effective, and far less invasive. A typical hospital stay is 36 hours or less, with return to normal activities within a week.

LLC requires four incisions: two half-inch-long cuts and two quarter-inch-long cuts. The laser energy is delivered along a tiny flexible quartz fiber through one of the larger openings, and is focused on a sapphire scalpel, which directly con-

tacts the tissue. The scalpel channels the energy, minimizing damage to nearby tissue. A miniature TV camera is threaded through a tube called a laparoscope inserted in the second large hole. The two smaller holes permit entry of surgical instruments. The procedure can be performed by one or two surgeons.

Postoperative pain, if any, can be controlled with over-the-counter painkillers rather than the narcotics often needed following traditional cholecystectomy. This latest "band aid" surgery (so-called because it requires tiny incisions) promises to be particularly beneficial for the elderly.

"Older people often cough more frequently than others, and in the past, they have suffered badly with a large abdominal incision," says Phillip Rosett, M.D., who performs LLC at Thorek Hospital in Chicago.

"With the bigger incisions [of traditional gallbladder removal], older patients have a greater risk of developing pneumonia. They also have greater difficulty getting out of bed. It usually takes 24 hours before they can move from the bed to a chair and close to another 24 hours to start walking again. However, with LLC, my patients are up and walking the same afternoon, and they walk out of the hospital the following morning," he adds.

It's nice to know that gallbladder disease is one problem for which treatment is becoming both simpler and more successful. Although the answers aren't all in on what causes gallbladder disease, it couldn't hurt to follow the advice of the American Heart Association and the National Cancer Institute and add more fiber to our diets and cut back on fat. ■

Ricki Lewis teaches biology at the State University of New York at Albany and is the author of Beginnings of Life.



No Safe Tan

by Alexandra Greeley

Ever since fashion designer Coco Chanel sported her new tan after a yachting vacation in the 1920s, many Americans have equated tanned skin with good health, great wealth, leisure time, social status, beauty, and high fashion.

In the January 1991 issue of *Vanity Fair* magazine, writer Bob Colacello interviews Hollywood heartthrob George Hamilton. Hamilton may well be most famous for his perpetual tan, which Colacello describes as "perfect, not too shiny or too dull, not too orange or too brown, but the same cinnamon wash he's had since he was sixteen."

During a television program, Hamilton tells viewers of how he grabs a tan whenever and wherever he can. One can only wonder why Hamilton and others like him have ignored the outpouring of information in the last decade from such sources as the Food and Drug Administration and the American Academy of Dermatology, the National Cancer Institute, and the American Cancer Society, which have been repeated by many fashion magazines. With a consistent message, experts are warning Americans of the hazards of exposure to ultraviolet radiation, the sun's UVA and UVB wavelengths. These imperil all sun worshippers—regardless of natural skin color—in ways that Coco Chanel could never have imagined.

To understand why sun damages, says Warwick Morison, M.D., associate professor of dermatology at Johns Hopkins

But further damage occurs at the cellular level, he explains. When the sun hits the skin, the DNA in the skin cells gets distorted. "Think of the DNA in the cell as a spiral staircase," he says. "What happens is that the two chains of the DNA are no longer connected and the stairs go off at a funny angle. Normal people have the enzyme that attempts to repair the damage." But, he adds, the repair is never total; some damage always remains, and it accumulates over the years.

While the immediate harm—the burning, blistering and peeling—is painful, what people should fear are the long-term consequences of regular sun exposure and tanning—those skin and other body changes that may appear as many as 20 or 30 years later, long after even the memories of carefree days of sunbathing have faded. Skin cancer is one consequence.

Most experts attribute the dramatic rise in skin cancers to America's love affair with the sun and to Americans' changed lifestyles that put people outdoors for longer periods, for more months of the year, and often in skimpier outfits that leave more skin exposed.

Skin Cancer Increases

There are three main types of skin cancer—melanoma, basal-cell carcinoma, and squamous-cell carcinoma. The deadliest of these is melanoma, but squamous-cell carcinoma is also a killer and the most common form of skin cancer among black Americans, reports Ted Rosen, M.D., associate professor of dermatology, Baylor College of Medicine at Houston.

University, think of yourself sitting unprotected on the beach for four hours. This sunbathing process kills skin cells by UV radiation and alters the function of collagen and elastin, the connective tissue in the skin. It also causes blood vessels to dilate. "That's why people turn red," he says. Days after you leave the beach burnt and blistered, you lose a layer of skin as it peels off. You may even freckle as a result of local changes in pigment cells. And those are only the acute, immediate changes.

Even tanning slowly and carefully is dangerous. Darrell Rigel, M.D., clinical assistant professor of dermatology at New York University, Manhattan, maintains, "There's no such thing as a safe tan. That's the key point. You have to think about why you tan. The body senses that it is being injured by UV radiation and, to protect itself, it produces melanin." (Melanin is the body's natural sun block, the dark pigment that skin cells produce to block out damaging rays and that cause tanning.)

According to the American Cancer Society, more than 600,000 people were diagnosed with basal-cell and squamous-cell carcinomas in 1990, up from 400,000 in 1980. Thirty-five thousand more were diagnosed with melanoma in 1990.

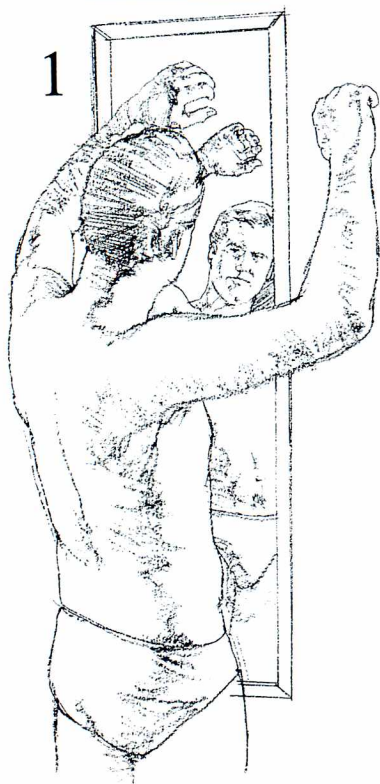
The rate of melanomas has doubled in less than a decade, says Vincent DeLeo, M.D., assistant professor and director of environmental dermatology, Columbia Presbyterian Medical Center, Manhattan. "It's already the number one cancer in young women under 35. And it's increasing rapidly." If not removed in the earliest stages, deadly melanomas do not carry a very good prognosis.

Melanomas can metastasize and appear in many sites, says Paul Bergstresser, M.D., chairman of the department of dermatology, University of Texas Southwestern Medical Center, Dallas. "Or they can migrate down the lymph system and can be in adjacent sites, so even if the original melanoma is removed, others may still be present. Or the original melanoma can be entirely removed and that's it." But, he adds, even someone who has had a melanoma successfully removed remains at risk of developing a second one.

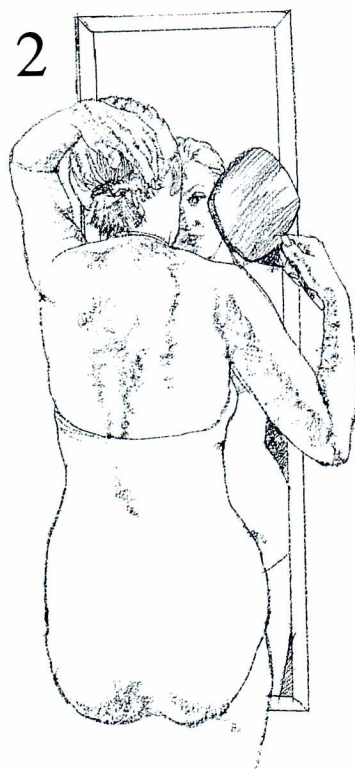
(Continued)

Monthly Self-Examination

1



2



1. Examine your body, front and back, in the mirror, then the right and left sides with arms raised.

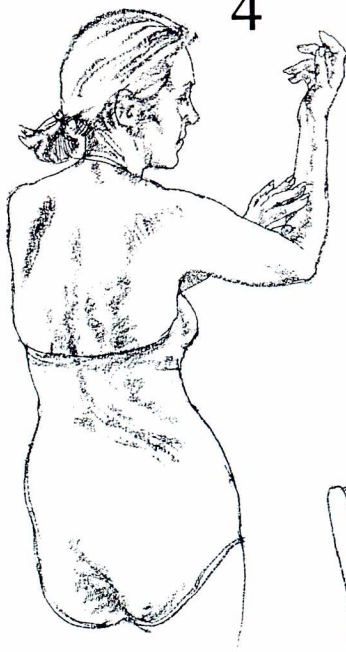
2. Examine back of neck and scalp with the help of a hand mirror—part hair (or use blow dryer) to lift and give you a close look.

3. Check back and buttocks with hand mirror.

3



4

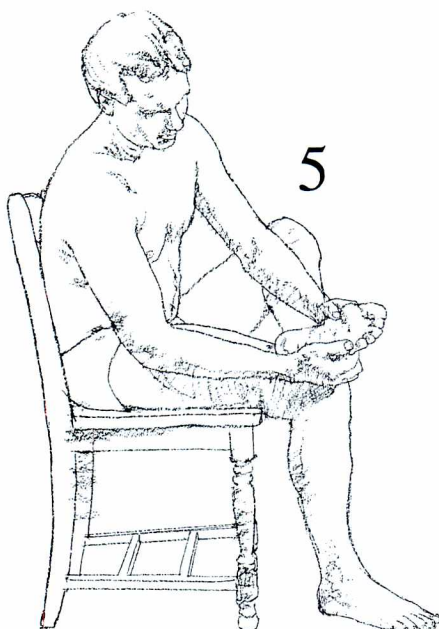


4. Bend elbows and look carefully at forearms, upper underarms, and palms.

5. Look at backs of the legs and feet, including the soles and the spaces between toes.

(Source: American Academy of Dermatology)

5



Why is melanoma on the increase? "It has been associated with sun exposure," says Bergstresser, "but the link to sunlight is not as logical. It is more complicated. Indeed, patients with melanomas are more common with more sun exposure in southern latitudes, but, also, melanomas may appear on body sites that are protected. Those people with the highest light exposure appear to have a lower frequency of melanomas than those who get sunlight more episodically," he says. Finally, those people who have had severe sunburns at an early age are also at higher risk for melanomas.

Not all melanomas seem to be related to sun exposure, however. The evidence linking sun exposure to melanoma is the strongest for the least common type of lentigo maligna melanoma. But the cause of melanomas in general, adds Arthur Sober, M.D., associate professor of dermatology at Harvard University, is still a controversial topic.

Sun Ages Skin

Cancer aside, sun exposure also ages the skin. Bergstresser tells the tale of a former neighbor, a 67-year-old woman whose face was marked with fissures, clogs and wrinkles. "It was very sad," he says. "She had been married to some movie distributor leader, and he had always encouraged her to get a tan. When she got old looking, he left her. Well, one day my father was visiting me, and spied her picking up her morning paper. He

came back in the house, calling her 'the old lady across the street.' The thing is, she was the same age as he." With suntans and skin aging, he adds, "There is a tomorrow. . . . These debts will be paid."

Premature skin aging follows a certain course, says Rigel. "At one end of the spectrum, you have freckling, and freckles are a sign of sun exposure. At the other end of the spectrum is skin cancer. These are not two separate processes. In between, you have lines, leatheriness, and precancerous actinic keratosis," he says.

Indeed, remarks Sober, to convince themselves about how the sun ages, people should look at the skin under the arm or on the buttocks. "It's beautiful, wrinkle-free skin," he says. "You'll see some intrinsic aging—it's thinner, and it heals less quickly. But if you stay out of the sun from early in life, by middle age you will look younger, perhaps by as much as 20 years."

UV radiation can damage the eyes as well. There is data on Chesapeake Bay watermen who spend large amounts of time on the water that show those who wore sun protection developed fewer cataracts, says Vincent Giovinnazzo, M.D., member of the American Academy of Ophthalmology's committee on sports ophthalmology and eye safety. "We feel that if you are out in the sun long enough to get a tan or burn, you should be wearing some protection for your eyes," he says.

Sunglasses

But not just any sunglasses will protect, no matter how expensive or glamorous they are. Basic sunglass labeling should help consumers make the right purchase. FDA and the Sunglass Association of America have agreed that manufacturers may voluntarily label sunglass products according to the performance standards set by the American National Standards Institute (ANSI) in New York, says Denis McCarthy, chief of FDA's surgical and diagnostic branch.

According to ANSI, sunglasses fall into three categories: cosmetic use—lightly tinted for wear in mild sunlight, to block at least 70 percent of UVB and 20 percent of UVA; general purpose—medium-dark tinted for most outdoor use, to block at least 95 percent of UVB and at least 60 percent of UVA; and special purpose—dark-tinted glasses for intense sunlight, to block at least 99 percent of UVB and 60 percent of UVA.

For the maximum eye protection, however, says Giovinnazzo, people need sunglasses that ensure 95 to 100 percent blockage of both UVA and UVB radiation. In addition, "Look for a wide frame that wraps around. Small glasses may be stylish, but they let lots of light seep in," he says. Cost is not a factor, he adds, because even some of the least expensive sunglasses can offer good protection.

Polarized glasses are good for cutting down on glare, but that does not necessarily mean they block out most UV light, nor does the darkness of the lenses in the eye wear mean much about UV blockage.

Finally, recent research shows that UV radiation not only suppresses the immune response of cells in the skin—which contributes to the growth of skin cancers—but may also induce generalized immune suppression and have an important impact on how people fight off infectious diseases, reports Margaret Kripke, Ph.D., chairman of the department of immunology, University of Texas, M.D. Anderson Cancer Center, Houston.

Some experts argue that the shorter, more energetic UVB rays—even though they are responsible for producing melanin and for thickening the skin's outer layer as protection against

sun damage—are more harmful because they damage cell DNA. "If the breaks in the DNA are not repaired correctly, the next generation of cells will have abnormal DNA that may reproduce cancer cells. Or they may just be cells that die," says Bergstresser.

Others, like Rigel, indict UVA, saying that it penetrates more deeply than UVB and it damages the dermis, the inner layer of skin that contains the blood vessels, hair follicles, and nerve endings—and ultimately this is responsible for skin aging. Further, adds Janusz Beer, Ph.D., D. Sc., of FDA's Center for Devices and Radiological Health, "In our laboratory, UVA is our prime interest. . . . If we take a cell culture and expose it to UVA radiation, we can see that these cells disintegrate. That may be happening when we are exposed while tanning and it may be happening in the bloodstream. . . . If what we see happening in our experiments happens in tissue, then you can certainly change much in the blood by disrupting white and red blood cells."

Tanning Devices

In the end, all experts agree that all sunlight—whether on the mountains or at the shore, on the equator or up north, at midday or midafternoon, in winter or summer—has the potential to damage human skin. And that includes artificial sunlight beamed out of the popular tanning devices that people often use year round in the mistaken belief that these devices tan safely. Manufacturers claim that newer models are safe because they emit only UVA radiation. But UVA itself can be damaging, and many of the UVA devices do emit UVB, "and it doesn't take much to cause damage," says Bergstresser.

According to a British study, says Morison, about 50 percent of those who go to a tanning salon to use a device have a skin type that really can't tan. "They go because there's something magic about it, about selling tans," he says. Others, says Sober, use tanning devices for an indoor "base" tan before taking a winter tropics holiday. Their intent is to protect themselves from future sunburns. But, he says, they are in for a surprise. A UVA tan does not protect well since it is distributed differently and scattered elsewhere throughout the skin, he says.

Many experts would cheerfully ban tanning salons, but, as Beer notes, that's impractical. "You can't ban beaches," he says. What FDA is doing is making sure the use of the equipment is as safe as possible by developing and enforcing regulations. FDA regulations on sunlamps, initiated in 1979 and amended in 1985, require, among other things, that sunlamps bear warning labels that say "Danger—Ultraviolet radiation" and advise users to avoid overexposure and to wear protective eye wear.

Sunscreens

While some people are heeding the messages about safe sun exposure, most experts acknowledge that many others pay no attention at all. Further, they realize that few people can totally avoid sun exposure. As a universal precaution, then, people should learn to wear a sunscreen regularly, particularly if they plan to spend any length of time in the sun. "You can be certain about it," says DeLeo. "If used correctly, sun blocks will reduce the likelihood and intensity of sunburn by blocking the UVB rays that create burns."

"Consumers can expect to get the kind of protection the labeling specifies," says William Gilbertson, Pharm.D., director of FDA's division of OTC drug evaluation. Generic sun blocks are just as safe as brand names, he continues, but urges con-

Skin Cancer Danger Signs

The American Academy of Dermatology advises: Know your spots and do a spot check. Also, have your skin checked by a doctor for any changes once a year. If you notice one of the following changes in your skin, you should see your family doctor or dermatologist immediately:

- **Basal-cell or squamous-cell carcinomas:** any lesion that is new, that starts growing, that starts changing, that bleeds, that is scabby, or that doesn't heal.

- **Melanoma:** Remember your ABCD's:

A. *Asymmetry:* One half of a mole or lesion doesn't look like the other half.

B. *Border:* A mole has an irregular, scalloped, or not clearly defined border.

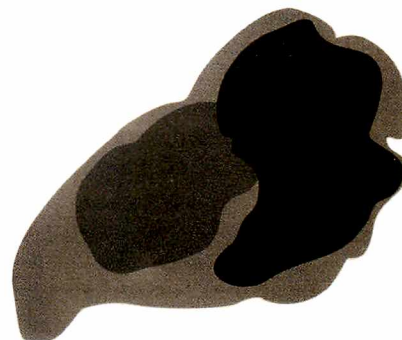
C. *Color:* The color varies or is not uniform from one area of a mole or lesion to another, whether the color is tan, brown, black, white, red, or blue.

D. *Diameter:* The lesion is larger than 6 millimeters or larger than a pencil eraser.

- **Actinic keratosis:** a precancerous skin lesion that is dry, scaly, reddish, and slightly raised. ■

—A.G.

Melanoma Warnings



Asymmetrical

sumers to be aware of product differences. Sunscreens are formulated differently so they may affect people's skin differently, he says. He also suggests that people buy a small container of sunscreen to start out—that way, they can determine whether the product feels good or irritates the skin.

Figuring out which sun protection factor (SPF) of sunscreen to use is an individual decision, says John DiGiovanna, M.D., investigator in the dermatology branch, National Cancer Institute in Bethesda, Md. "The best way to judge the number? For example, if you select an SPF of 15, realize that that means you can stay out in the sun 15 times longer than if you were wearing no sunscreen, and still get the same amount of redness," he says. "Most importantly, you should find something that feels comfortable—a solution, lotion or cream—and apply it daily before you go out. Many women recognize that this is the way to prevent photo-aging and they will use a sun block before they put on their makeup."

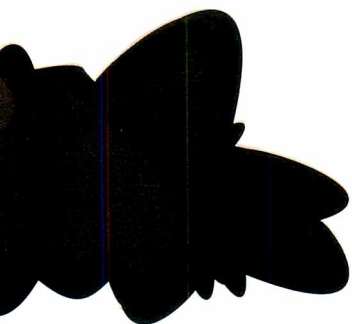
The American Academy of Dermatology and the National Institutes of Health agree that people should wear a sunscreen with an SPF of 15 or higher. But some experts wonder if sunscreens with SPF higher than 30 really make any sense.

According to Gilbertson, FDA will probably propose that 30 is the highest SPF people would need, but he adds that manufacturers are still free at this time to market sunscreens with higher numbers because these are still being evaluated. Which ever product consumers select, he adds, they should apply sunscreens liberally—beginning before exposure—and often. This advice applies to everyone, regardless of natural skin color.

Even though the risk of skin cancer for naturally brown- and black-skinned persons may not be as great as for light-skinned individuals, those with dark skin should also apply sunscreens, especially during long periods of sun exposure.

Children should also wear sunscreens. "Most skin cancers begin in childhood," says Sydney Hurwitz, M.D., clinical professor of dermatology and of pediatrics, Yale University School of Medicine. "And the greatest exposure—50 to 80 percent of a person's lifetime exposure—to the sun occurs during childhood, by the age of 18." Studies show that a history of painful or blistering sunburn during the first 10 to 20 years of life doubles the risk of skin cancer. "We've got to convince teachers, parents, doctors, coaches, counsellors, and children that protection from overexposure to the sun is important. For children, putting on a sunscreen should be just like brushing their teeth everyday," he says.

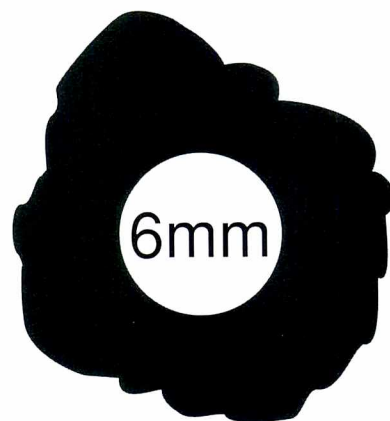
For people who still want to tan despite the danger, DiGiovanna advises getting sun exposure gradually and using some sort of sunscreen. Or DeLeo mentions commercial products that "tan" the skin without the sun. He describes three: "There's a skin bronzer that's like putting on lipstick. It's perfectly safe unless you are allergic to its components. There's a tan accelerator which contains tyrosine, a protein that produces melanin. It doesn't work, and it's a waste of money. Or there's a skin dye, which contains lawsone. This goes on clear, binds to a protein in the skin, and turns color overnight. It looks like a tan, but is not really a tan," he says. Products that contain tyrosine and lawsone when used as a skin dye have not yet been approved by the agency. Gilbertson



Border irregular



Color varied



Diameter larger than 6mm

says that FDA has banned—or has proposed banning—most tanning pills. But bronzers that contain approved FDA color additives such as dihydroxyacetone are safe to use, says John Wenninger, associate director for cosmetics of FDA's division of colors and cosmetics.

Check for Changes

And everyone, whether they sunbathe or not, should check their skin regularly for changes that might spell trouble. (See accompanying article.) They may also want to take advantage of the month-long Melanoma/Skin Cancer Screening Program sponsored by the American Academy of Dermatology. This public awareness effort, which makes screening available in many communities nationwide in May or June each year, is an appeal for early detection and screening of skin cancers.

"It's a great public service," says Howard Koh, M.D., associate professor of dermatology, medicine, and public health at Boston University Schools of Medicine and Public Health, and chairman of the American Academy of Dermatology's committee on Melanoma/Skin Cancer Screening Programs. He reports that since 1985, the American Academy of Dermatology has screened 359,000 people and has detected over 2,500 suspected melanomas and almost 29,000 suspected non-melanoma skin cancers. "The good news is," he says, "that melanomas and skin cancers are an area in which screening and prevention can make a difference."

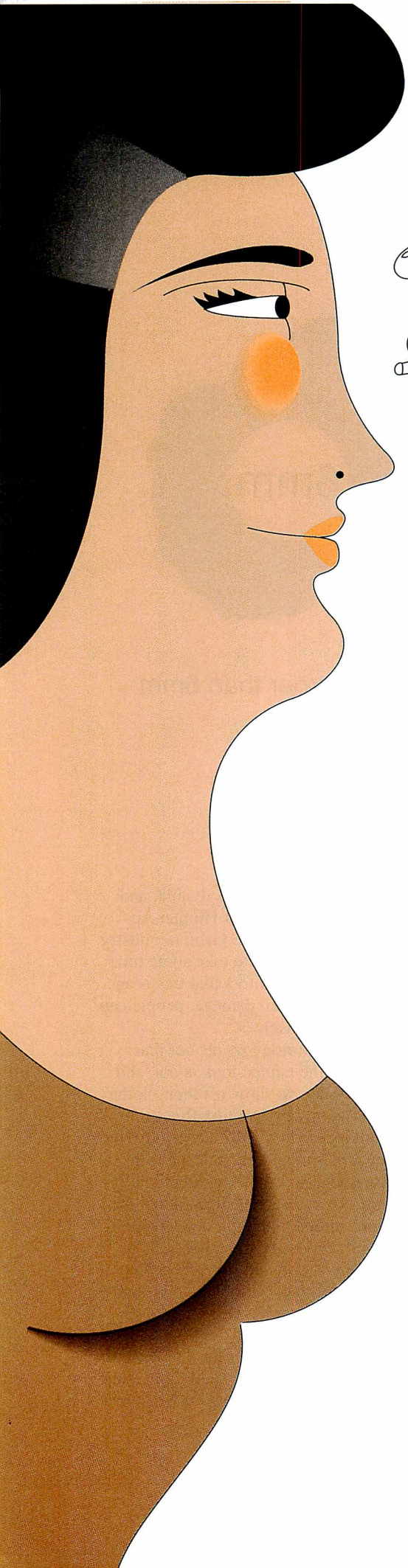
To turn the tide against sun damage, people must learn to think of pale skin as attractive, says Michael Pertschuk, M.D.,

clinical associate professor, University of Pennsylvania, and chief of psychological services at its Center for Human Appearance. As it has in the past, he believes the fashion industry can alter people's behavior. "It's just going to take some time and an awareness on the part of fashion editors that this is an issue," he says. Once convinced about sun damage, people can act in a reasonable way to protect themselves.

The American Academy of Dermatology points out that many fashion designers think that the tanned look is out, and they are using lighter-skinned models to show off their clothes. But two studies done for the academy by Opinion Research show that not everyone is convinced: In a 1987 survey of over 1,000 people on attitudes towards sunbathing, half the teenagers and 45 percent of those under 35 said they intentionally worked on a tan. A follow-up survey in 1989 showed that the figures remained basically unchanged, although people admitted they knew that sun exposure was bad for their skin. But among adults, at least, sunscreen use was up from 35 percent to 41 percent. And Pertschuk believes that older women probably are avoiding the sun more because they are beginning to see their own skin damage show up.

In the end, there really is nothing new under the sun, except that perhaps more people are staying out of it, heeding medical warnings such as Bergstresser's: "Less sun is better. No sun is best of all." ■

Alexandra Greeley is a writer in Reston, Va.



Trying to Outsmart Infertility

by Judith Randal

The human female is born with about a million eggs—all that she will ever have. Beginning with the onset of menstruation in adolescence and continuing until menopause, her hormones prepare one or two of these eggs for possible fertilization each month. The human male, starting at puberty, makes many millions of sperm a day for the next 50 years or more. Biology, it would seem, generously equips both sexes for parenthood. Yet the National Center for Health Statistics reports that roughly 1 of every 12 American couples that tries to have a baby fails.

Sometimes, the problem is simply impatience. Medically speaking, a couple generally isn't termed infertile unless there is still no baby on the way after at least a year of regular intercourse without using any form of birth control.

The odds are sharply against conception most of the time. A woman has just a 20 to 35 percent chance of conceiving during each menstrual cycle, even at the peak of her fertility, and that starts to decline slightly in her late 20s and early 30s and more steeply after about age 35. For the many members of the baby boom

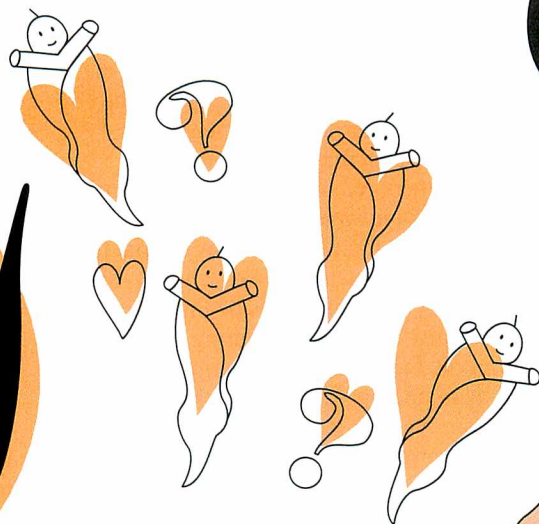
generation in particular who are late in trying to start families, getting pregnant is not necessarily as easy as the proverbial fall off a log.

The other variable in the childbearing equation is male fertility, which, like female fertility, declines with age, although more slowly.

Fertility is impaired in as many men as women. More specifically, according to Robert D. Visscher, M.D., medical director of the American Fertility Society, the problem lies entirely with the man in about a third of infertile couples and entirely with the woman in about another third. In another group of such couples—some 15 to 20 percent of the total—the fertility of both the man and the woman is below par. There are, besides, couples in whom nothing can be found in either partner to explain the reproductive difficulty. Would-be parents can therefore avoid a lot of heartache by thinking of infertility as “our” problem rather than “mine” or “yours.”

Health professionals, too, are coming to recognize the importance of this no-fault philosophy. “The realization that the infertile couple is a unit is probably the greatest advance medicine has made in this field,” said Elwyn Grimes, M.D.,

ertility



a Kansas City, Mo., reproductive endocrinologist who serves on a Food and Drug Administration obstetrics and gynecology advisory panel. "When a couple is having trouble having a baby and decides to try to do something about it, it makes no sense to evaluate one partner and not the other. Besides, efforts to overcome infertility require the cooperation of both partners and so put both under considerable emotional stress."

Perhaps most stressful of all is the knowledge that those efforts may come to naught. Systematic studies to determine how often treatment results in a successful pregnancy have not been done. But the consensus of the experts, says the American Fertility Society's Visscher, is that the success rate is, typically, in the 50 percent range. Moreover, a pregnancy is no guarantee that a baby will be born. There is always the possibility of a miscarriage or other complication during the nine months of gestation that will leave a couple with a cradle as empty as before.

Identifying Stumbling Blocks

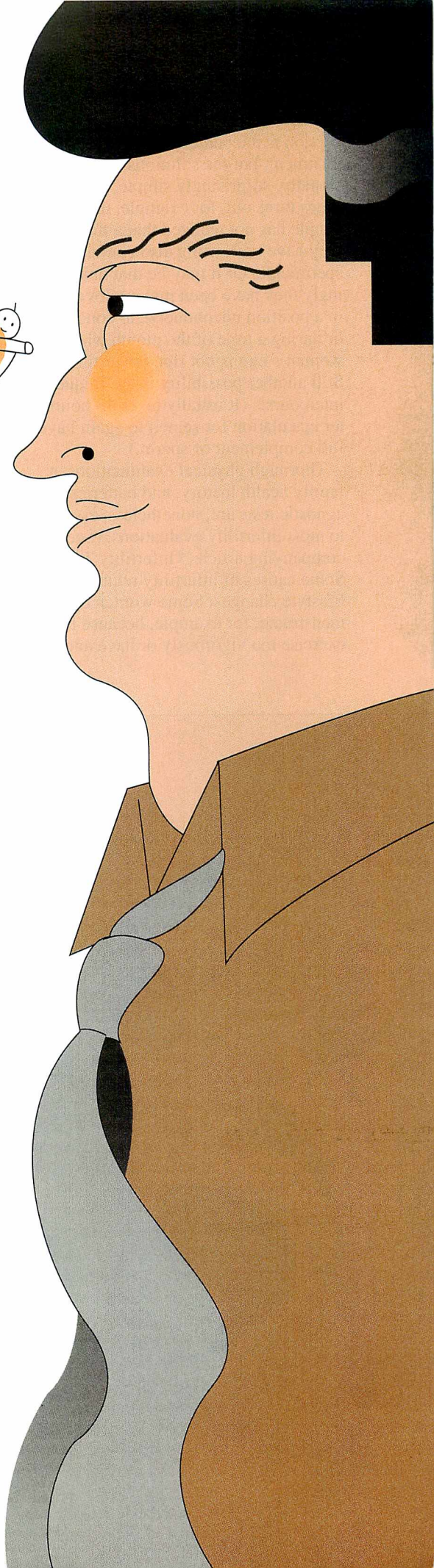
The mishaps that can befall a pregnancy aside, the biology of setting one in motion is itself enormously complex.

(See diagram.)

Pregnancy cannot occur unless it is preceded by a long series of hormonally controlled interactions that separately prepare sperm and egg for their missions. A woman will not conceive unless her partner is able to deposit semen in her vagina and his sperm are sufficiently vigorous so that at least one can swim into her fallopian tubes to fertilize a waiting egg. (Each of the two ovaries has its own fallopian tube that leads to the uterus. Because the ovaries normally take turns releasing an egg, each of the tubes normally has an egg in it every other month.)

At the same time, the female must be in hormonal readiness to permit egg and sperm to unite when they meet in the tube, and the tube must be open from end to end. In addition, the muscle of the tube and the eyelash-like hairs on its lining (called cilia) must have enough strength and range of motion to sweep the egg into the uterus after it is fertilized. Even then, the fertilized egg will die if it does not implant in the lining of the uterus and if that lining—which is also under hormonal control—is unable to sustain it.

The considerable progress made in



identifying the stumbling blocks to conception is the bedrock of advances in treatment, but the solutions are, occasionally, surprisingly simple. It sometimes turns out, for example, that a couple has not realized that a lubricant they have been using also contains a spermicide. Or it may be that unknowingly they have been making love either in a position un conducive to conception or during a time of the month when the woman's egg is not ripe for fertilization. Still another possibility is too frequent intercourse. (It usually takes 48 hours after ejaculation for semen to again have a full complement of sperm.)

Thorough physical examinations, a family health history, and batteries of diagnostic tests are, nonetheless, essential to most infertility evaluations. (See accompanying article, "Infertility Tests.") Some causes of infertility require only lifestyle changes. Some women don't menstruate, for example, because they exercise too vigorously or have anorexia

or another eating disorder that has made them far too thin. For them, less activity or a more nutritious diet leading to weight gain may do the trick.

In men, reduced sperm activity may result from wearing clothing that keeps the testes too warm (jockey shorts, for instance, instead of boxer shorts). Sperm quality can sometimes be improved and fertility attained by wearing a water-cooled testicular hypothermia device, available by prescription, that FDA has approved for lowering the temperature of the scrotum.

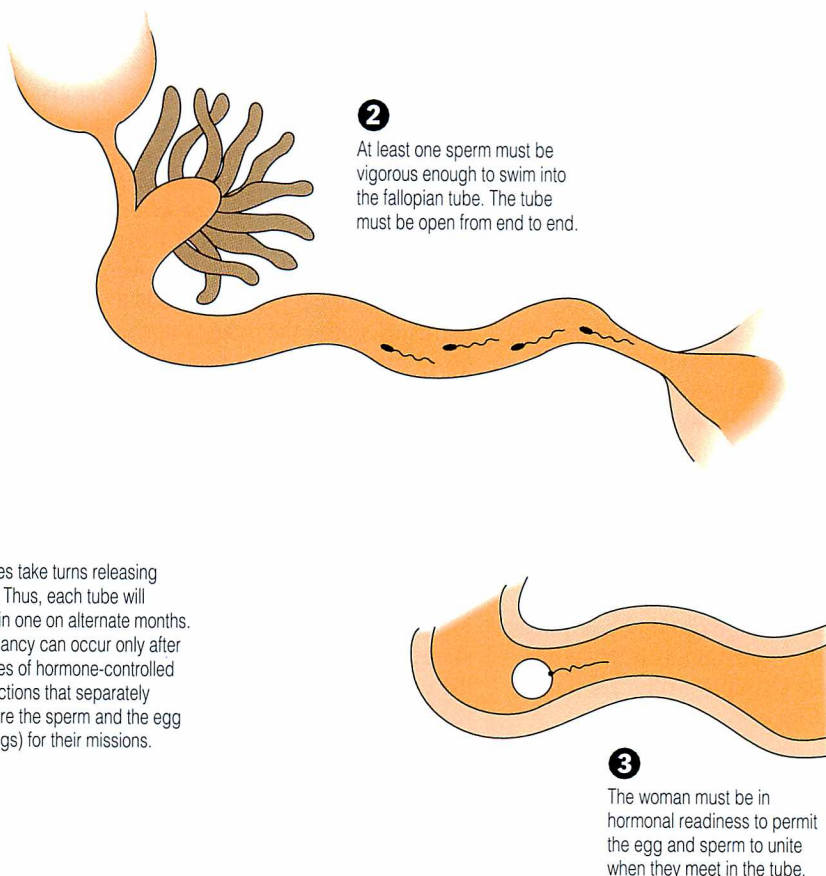
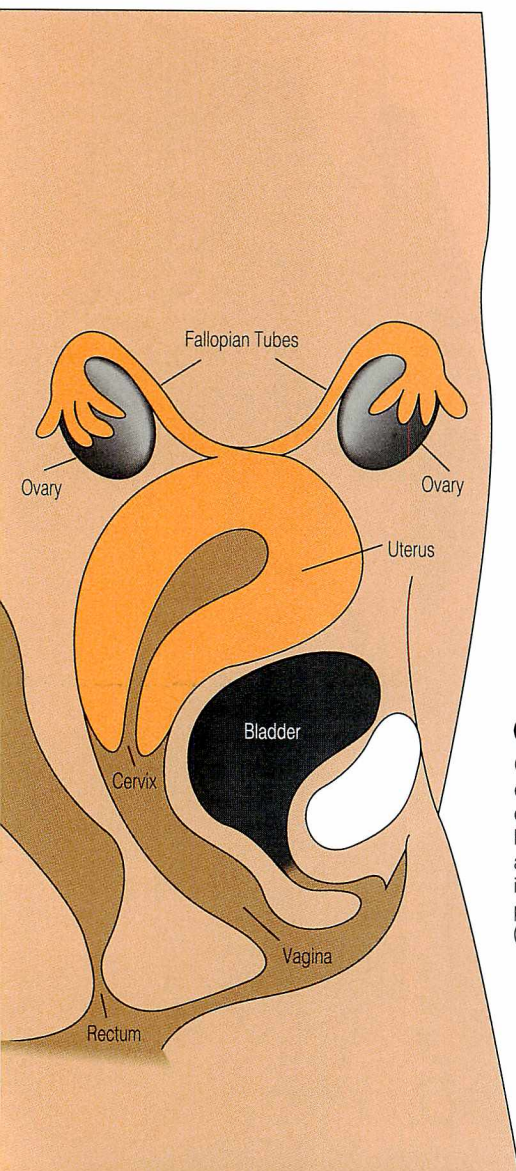
Fertility Drugs

Deciding what to do, if anything, when the evaluation is complete may not be easy. Assuming these problems are treatable—and not all of them are—there is a bewildering array of choices, especially for women, and no guarantee that any of them will work. So it is that specialists in this field speak of "maximizing fertility potential" rather than "curing infertility."

Fertility potential starts in the brain, in an area called the hypothalamus. In both men and women, a hormone made by the hypothalamus travels via the blood to the pituitary gland at the base of the brain. This gland in turn makes hormones of its own that circulate in the blood and act on the reproductive organs.

In males, the message received by the testes causes them to make still another hormone, testosterone, which is their signal to make sperm. In females, an analogous cascade of hormones distributed by the bloodstream plays an equivalent role in ensuring that the right chemical messages get to the right places at the right times to allow women to ovulate and conceive.

When blood and urine tests of an infertility workup suggest some sort of hormone imbalance in one or both partners, corrective therapy with so-called fertility drugs is frequently prescribed. The most popular of these drugs are Clomid and Serophene (both clomiphene citrate in



tablet form), which act on the hypothalamus, and Pergonal (human menopausal gonadotropins), which acts on the pituitary gland.

Because these powerful drugs can have a wide range of side effects, patients should always discuss the pros and cons of their use with the physician in advance. Clomid and Serophene, for example, can prolong the menstrual cycle and so make a woman mistakenly think she has conceived. Moreover, there is a risk with some fertility drugs of multiple births. Even if the couple would welcome several babies, multiple births can complicate pregnancy and delivery and endanger infant survival.

Surgery

Surgery is another tool often used to treat infertility in both men and women.

Many men have varicocele, a collection of swollen veins in the scrotum that often looks and feels like a bag of worms, but may be less obvious. Some

men with a varicocele easily sire children and so are clearly fertile. For those who seemingly are not and whose sperm are sluggish, surgical repair of the varicocele may better their chances of fatherhood.

However, according to Larry Lipshultz, M.D., professor of urology at the Baylor University College of Medicine in Houston, there is a debate among physicians about when the operation is appropriate. He does not, therefore, usually recommend it to his patients unless he is unable to find other reasons for their infertility.

Another male infertility problem often treated by surgery is damage to the vas deferentia, through which sperm must pass for ejaculation. A common cause of such damage is vasectomy, male sterilization. Though it should be considered irreversible, some men later wish to have it reversed. This is sometimes possible through microsurgery. Other candidates for such surgery are men whose vas deferentia have been blocked by scar tis-

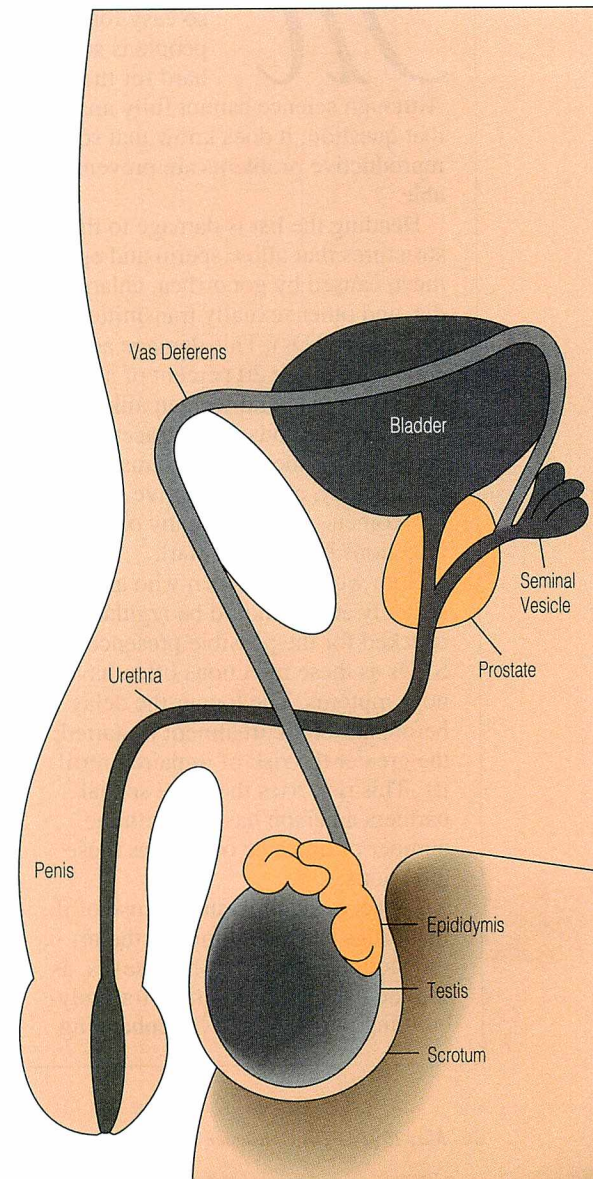
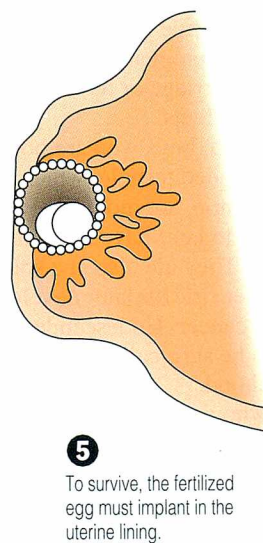
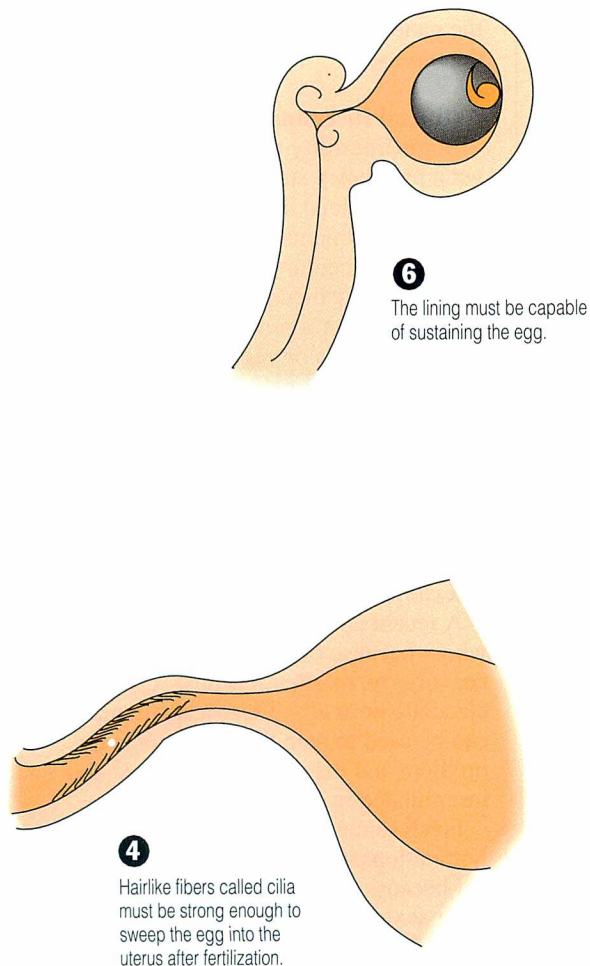
sue caused by earlier unrelated surgery or a sexually transmitted or other infection.

Microsurgery is not a cure-all, however. It cannot help men with extensive damage to these structures, and many with limited damage may not be able to father a child, despite the operation's apparent success.

A sterilization procedure for women, tubal ligation, involves tying, cutting or burning the fallopian tubes and so scarring them. Damage to the tubes by earlier unrelated surgery or infection—again, sometimes sexually transmitted—can also cause female infertility.

In both cases, corrective surgery is sometimes, but not always, a possibility. Nor do seemingly successful surgical repairs of damaged fallopian tubes necessarily mean that any eggs fertilized in them will be able to make their way to the uterus.

Sometimes, instead, an ectopic (literally, out-of-place) pregnancy occurs, in



Preventing Reproductive Problems



Many infertile couples wonder why something so easy for most people is so hard for them.

Although science cannot fully answer that question, it does know that some reproductive problems are preventable.

Heading the list is damage to the structures that allow sperm and egg to meet, caused by gonorrhea, chlamydia, and other sexually transmitted diseases (STDs). This damage accounts for about 20 percent of all infertility in men and women alike. Use of barrier methods of contraception—condoms for men, diaphragms (with spermicide), or contraceptive sponges for women—can stop many of these infections before they start.

Both women and men who are sexually active should be regularly checked for the possible presence of STDs as these infections often have no symptoms. The longer the delay before antibiotic treatment is started, the greater the risk of impaired fertility. This risk rises the more sexual partners a person has and with the number of times he or she has these infections.

Tobacco, alcohol, and the use of illicit drugs can also diminish the reproductive potential of both sexes, as can the use of steroid drugs for bodybuilding purposes and for enhancing

sports performance. So can poor nutrition, rapid weight loss, and either too much or too little body fat. The same goes for excessive rigorous exercise, meaning more than an hour a day. While too much exercise is more likely to impair female than male fertility, neither sex can count on escaping its reproductive effects.

Childhood immunizations also have a bearing on future fertility. Immunization against mumps and rubella (German measles) is particularly important because the male who gets mumps in adolescence or later runs a high risk of becoming permanently sterile, and the female who gets rubella while pregnant—particularly early in pregnancy—is at high risk of miscarriage or having a baby with birth defects.

In addition, boys who are born with an undescended testicle, which is fairly common, are more likely than other boys to later have reproductive problems. They are also at a somewhat higher risk for later developing testicular cancer. Undescended testicles can be surgically corrected during childhood.

Girls who don't menstruate by age 16 or are plagued with menstrual problems need to be evaluated by a physician. Neither condition is necessarily an indication of impaired fertility, but it is also true that delaying needed treatment can sometimes make the situation worse. ■—J.R.

which the fertilized egg gets trapped in the tube where it cannot survive when it grows. Any woman can have an ectopic pregnancy, but those whose tubes have been damaged are at greatest risk, even after corrective surgery. Although surgical repair of the damage lowers the risk of having an ectopic pregnancy, it remains higher than for women with tubes that have never been damaged.

Endometriosis, a common disorder in women, also can cause or contribute to infertility when small pieces of the uterine lining escape and take up residence on the surfaces of organs in the abdominal cavity.

Inflammation and consequent chronic irritation from the misplaced tissue can eventually so badly scar the ovaries, fallopian tubes, inner or outer walls of the uterus, or other nearby structures that the woman cannot conceive. (See "Endometriosis: A Growing Cause of Infertility in Women" in the March 1986 *FDA Consumer*.)

Both surgery and drug treatments, sometimes combined, are used to treat endometriosis. Success rates in the hands of a physician skilled in treating this disorder are in the 50 to 60 percent range, and depend on several factors, including the patient's age and manifestations of the disease.

Artificial Insemination

Some infertility treatments attempt to get a pregnancy started without intercourse. Artificial insemination, the oldest of these treatments, has been used for more than a century. A hollow, flexible instrument—called a catheter—is used to place the donor's semen into the woman's uterus or vaginal canal.

All inseminations are performed around the time the woman should be ovulating, either naturally or after priming with a fertility drug. The semen may be from the woman's husband ("artificial insemination-husband," or AIH, for short) or from an anonymous donor ("artificial insemination-donor," or AID).

A recent advance in AIH is for men who—because of spinal cord injury, cancer surgery, or other reasons—can't ejaculate normally. Electrical stimulation can be used to help them overcome this problem and the ejaculate collected and inseminated in their wives.

Fresh semen was once used for all inseminations and still is, as a rule, in AIH, but because of concern about AIDS and other sexually transmitted infections, FDA, the Centers for Disease Control,

and the American Fertility Society now recommend that anonymous donor semen be frozen for at least 180 days before use. The delay allows the donor semen to be retested for possible infection.

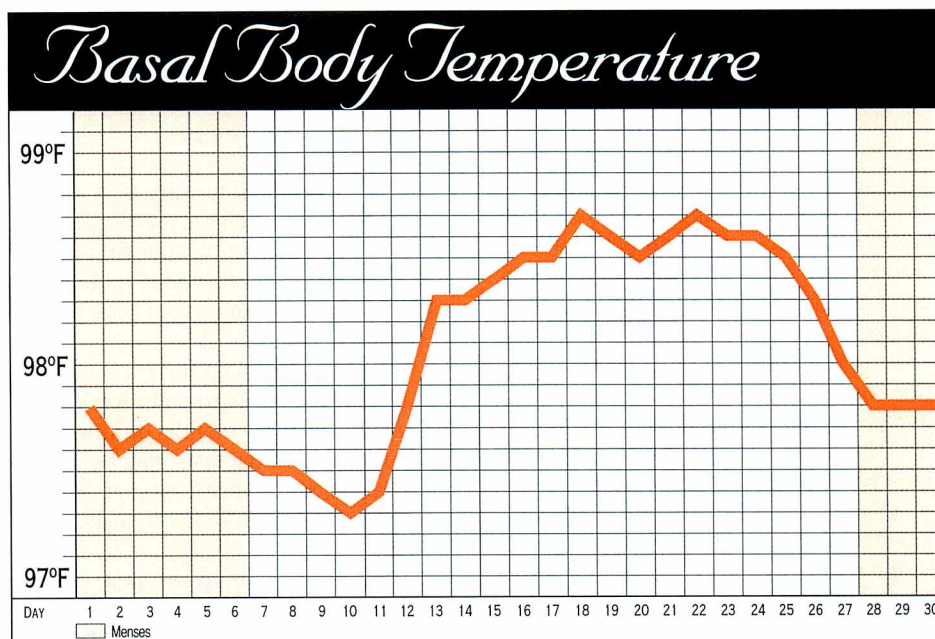
Some women become pregnant with one insemination. More often, repeat inseminations over the course of four to five menstrual cycles are required. And there are women who after a year or more of periodic insemination still do not conceive. Depending on the nature of the couple's infertility, studies show success rates between 50 and 65 percent.

In Vitro Fertilization

Much newer than artificial insemination is *in vitro* fertilization (IVF), made famous by the birth in England in 1978 of Louise Brown, the world's first "test tube" baby. IVF is an option when various other treatments have failed or are inappropriate. It can be used, for example, in women who have a uterus and at least one ovary, but whose fallopian tubes are damaged, missing or diseased.

The woman is prepared for this procedure with fertility drugs that ready several of her eggs for fertilization and the lining of her uterus to support a pregnancy. The eggs are then taken from her by one of several methods and placed in a laboratory dish where they are incubated with her partner's sperm for about 18 hours.

Assuming that some are fertilized and continue to develop normally for two days or so, one or more (as a kind of insurance policy, it is usually several) are transferred by instrument into the woman's uterus. If at least one implants



This chart shows an example of how a woman's temperature, as measured before getting out of bed in the morning, varies with her menstrual cycle. Temperature is lower in the first half of the cycle, beginning with onset of menstruation. The substantial sustained rise beginning on day 13 indicates ovulation has probably occurred. Such charts can help couples calculate when conception is most likely.

there within about two weeks, the woman is pregnant. Implantation can often be determined at that time by a blood test. However, this chemical assessment is sometimes misleading. Therefore, a conclusive diagnosis cannot be made until a week more or so has passed when—if the pregnancy is real, rather than just chemical—a sac will have formed around the embryo that can be detected by ultrasound.

As with other infertility treatments,

couples undergoing IVF should not count their chickens before they hatch. In a study published in 1988, for example, 41 clinics that had treated 3,055 women with one or more cycles of IVF reported that only 485 (15.9 percent) became pregnant and just 311 (10.2 percent) delivered a living infant.

Still Newer Techniques

Newer still than *in vitro* fertilization are several other techniques that also require the use of fertility drugs. They are:

- **Gamete Intrafallopian Transfer (GIFT):** Similar to IVF except that sperm and eggs are collected and immediately inserted into one or both fallopian tubes, where conception occurs. Unlike IVF, GIFT requires that the woman have at least one healthy fallopian tube. Success rates are similar to those of IVF.
- **Tubal Ovum Transfer:** The woman's eggs are retrieved and put into the fallopian tube close to where it opens into the uterus. The couple then has intercourse or the woman is artificially inseminated. Since this method allows the eggs to be placed beyond the parts of the tube that may be damaged or blocked, it can often be used when GIFT cannot.
- **Embryo Lavage:** A fertile female donor provides the eggs. At the proper time in her menstrual cycle, she is artificially inseminated with the would-be father's

Choosing a Doctor

Rather than relying on advertisements or affiliations, when choosing a physician for infertility services, it is wise to check on his or her qualifications. The local medical society can usually provide background information on the doctor you are considering consulting.

For women, the right physician will probably be a board-certified obstetrician-gynecologist and may well be one who, besides, has had two years of further training in reproductive endocrinology.

For men, the right doctor will likely be a board-certified urologist with a special interest in infertility. Often, such a urologist has had a fellowship in male reproductive problems in addition to his basic training in urology.

Resolve, Inc., a nonprofit organization, has a nationwide list of specialists for both men and women and information about all aspects of infertility care. Write: Resolve, Inc., 5 Water St., Arlington, Mass. 02174; phone (1-800) 662-1016. Many communities have Resolve chapters listed in local telephone books. ■

sperm. If the donor conceives, the early embryo is washed out of her reproductive tract and transferred to the uterus or a fallopian tube of the woman who is to bear the child. The recipient, meanwhile, has been hormonally treated with fertility drugs to make her uterus receptive to the embryo. This technique allows women who have no eggs of their own to become pregnant—provided they have a uterus.

• **Surrogate Motherhood:** This is an option for women who do not respond to ovulation induction therapies or who have no ovaries or lack a uterus. It also may be an option for those for whom pregnancy might be life threatening or have good reason to worry that they might transmit a serious genetic disorder to the child.

A healthy, fertile woman agrees to be artificially inseminated and also agrees to let the infertile couple adopt the baby. If the female member of the infertile couple can safely provide eggs of her own, these can be fertilized by the IVF process and then transferred to the surrogate woman who carries the fetus to term. In that case, the surrogate mother takes fertility drugs to prepare her uterus. Surrogate motherhood is controversial and has resulted in court cases about custody and parentage, which is rare with other forms of fertility treatment.

When to Stop?

If efforts to have a baby are unsuccessful, the question ultimately arises, “When do we stop trying?” Though it may not be easy, giving up the effort can have a happy ending, as is clear from the stories of two couples who met through a small social group in a distant suburb of Washington, D.C., and learned about their mutual interest during casual conversation.

The first couple had tried almost everything, including IVF, and, after 10 years of getting nowhere, gave up medical interventions. Two cycles later the woman conceived and—after a difficult pregnancy—bore a healthy baby girl. The other couple took a different route that is available to many couples who abandon hope for a child of their own. They adopted a newborn baby and now wish they had done it a lot sooner. ■

Judith Randal, a freelance writer in Lovettsville, Va., writes a weekly health feature for Newsday and has published widely on health and science subjects in other newspapers and magazines.

Infertility Tests

Some infertility tests are for women only, others are for men only, and still others cannot be done without the cooperation of both partners.

An initial workup for a woman can take as little as six to eight weeks, or as much as three months or longer because some of the tests may have to be repeated for verification at different specific times in her menstrual cycle.

The initial workup of a man usually can be done faster both because men have no monthly cycles—and because there are fewer tests for men. Diagnostic surgical procedures may be suggested for both men and women to look directly at reproductive structures and to obtain small tissue samples for laboratory analysis.

His

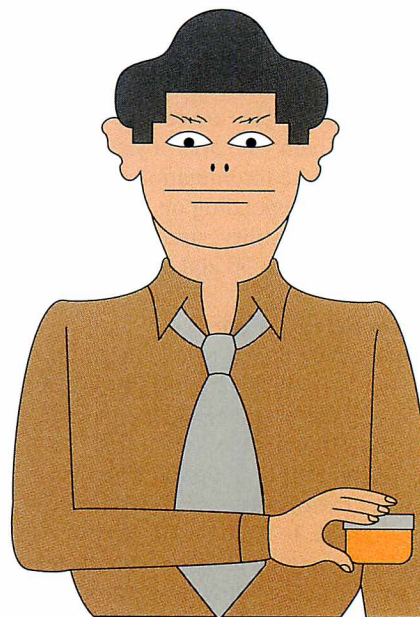
A semen analysis is almost always the first test done on men and is usually repeated several times. After abstaining from intercourse for about 48 hours, the man collects a sperm sample in a container.

The sample is microscopically examined to determine the number, activity and shape of individual spermatozoa (sperm cells) and the characteristics of the fluid part of the semen.

A healthy, potent ejaculate typically contains 1.5 to 5 cubic centimeters (5 cc = 1 teaspoon) of semen and each cc will contain an average of 70 million sperm that look to be of normal size, shape and behavior. If the specimen markedly differs on any of these factors, further tests may be done to determine whether infection, hormonal imbalance, or another problem could be the culprit.

Among these tests may be a testicular biopsy, a minor operation—performed with a local or general anesthetic—in which a small amount of tissue from the testes is removed for laboratory studies. Since even men with sperm counts well below 70 million per cubic centimeter sometimes father children, this test is ordinarily done only when the count is zero.

If damage to one or both of the vas



deferens, is known or suspected, an x-ray examination may also be ordered. As an iodine-containing solution has to be injected into the tubes to make them visible on x-rays, the patient is first given local or general anesthesia. If the examination discloses damage, surgical repairs are often attempted at the same time the diagnosis is made.

Other special tests may be ordered if none of the tests already mentioned seems to explain the man's infertility. The most common of these tests are the bovine mucus test and the hamster-oocyte penetration test.

In the first, bovine (cow) mucus (from the cervix, or neck of the uterus where it opens into the vagina) is placed in a special glass column. Samples of the man's semen are applied to the column, and measurements are made of how well the sperm are able to enter and swim through the mucus, giving some indication of their ability to swim through human cervical mucus.

In the hamster-oocyte penetration test, some of the man's semen is mixed with hamster egg cells that have had their outer shells (membranes) removed. If the sperm are functioning normally, they will penetrate the hamster eggs, an indication that they are also capable of fertilizing human eggs. However, failure of the sperm to penetrate the hamster eggs does not always mean that they are in-

capable of fertilizing human eggs.

Hers

Women-only tests, more varied and extensive, generally begin with a determination of if and when the woman is ovulating. One of the most popular techniques for pinpointing ovulation relies on the typically slight rise in resting body temperature midway in the menstrual cycle, signaling that ovulation has recently occurred.

A woman's body temperature fluctuates throughout her menstrual cycle, and she is instructed to record these fluctuations on a chart after taking her temperature each morning before getting out of bed. If the chart—called a basal body temperature, or BBT, chart—indicates that the woman has been ovulating, it can often be used to predict when ovulation will happen during subsequent menstrual cycles. The couple can then use the information to attempt to time conception. Several urine test kits, approved by the Food and Drug Administration for sale over the counter, can be used by consumers to supplement the temperature chart.

Still other methods widely used to predict ovulation rely on examinations of the cervical mucus, which undergoes a series of hormone-induced changes at various times in the menstrual cycle. Some versions of these tests require a health professional's expertise. There are, however, versions of them that some women—with a physician's guidance—can learn to do themselves.

Other methods widely used to diagnose female infertility and to monitor therapy include:

- **Endometrial Biopsy:** A long, hollow tube is passed into the patient's uterus late in her menstrual cycle, and a little of the lining is scraped off and examined with a microscope. The examination helps the physician tell whether the development of the egg and of the lining are in proper phase with each other. In most cases, the scraping is done in a physician's office and because it is only very briefly painful no anesthetic is used.
- **Ultrasound:** This technology relies



on sound waves to produce images of internal structures. It is used, often in combination with one or more of the tests already discussed, to find the presence or absence of follicles that contain and release the eggs. Ultrasound is also sometimes used to detect abnormalities in the ovaries or uterus.

- **Hysterosalpingogram:** This is an x-ray study of the uterus and fallopian tubes. It is done just after a woman's menstrual period so there is no danger of her being pregnant and thereby exposing the fertilized egg or embryo to radiation.

A dye containing iodine—technically called a contrast medium—is injected through the cervix. It spreads into the uterus and the fallopian tubes, allowing them to be visualized.

Among other things, this study often enables the physician to determine if the fallopian tubes are open. It is usually done without an anesthetic in the x-ray department of a hospital or clinic.

- **Hysteroscopy:** The patient's uterus is filled with a liquid or gas, instilled through the cervix. A thin, lighted tube called a hysteroscope that works like a telescope is then inserted into the uterus through the cervix, enabling the surgeon or physician to look directly inside. Many hysteroscopes have a separate channel through which instruments can be

passed, often making it possible to immediately correct any abnormalities. Patients undergoing hysteroscopy are usually given an anesthetic, which may be local or general.

- **Laparoscopy:** A laparoscope, like a hysteroscope, is an instrument with a light that works like a telescope. It is slipped into the abdominal cavity through a small incision in or near the navel. For a clearer view of the woman's reproductive tract, the cavity is filled with gas during the procedure, and a colored solution—usually blue—is injected into the uterus and fallopian tubes. A general anesthetic is required. Advanced operative techniques may allow the repair of defects in the reproductive tract to be made at the same time as the examination.

Theirs

Some tests require participation of both partners, as they have to be done after intercourse, which has to take place at the most fertile time in the woman's cycle. During the tests at a doctor's office, 2 to 12 hours after intercourse, several samples of cervical mucus are taken. Laboratory analysis determines whether sperm and mucus have been able to properly interact.

There are also a variety of tests that are used when the doctor suspects that infertility may be due to the man's forming antibodies against his own sperm or the woman's forming antibodies against them. The exact nature of these immunological problems is not yet well understood, but their detection is sometimes helpful in explaining why a couple is having reproductive difficulty. Some of these tests require the participation of both partners; others either one or the other.

A final word about all infertility tests: It is always best to ask in advance why they are being suggested, what they may show, how definitive they are, what the possible remedies are for any problem they may disclose, and what side effects or complications are possible from a given test. Many of these tests have potential risks as well as potential benefits.

■ —J.R.



Beware the Unknown Brew

Herbal Teas and Toxicity

by Sharon Snider

*There was an Old Man of Vienna,
who lived upon tincture of senna;
When that did not agree,
He took chamomile tea,
That nasty Old Man of Vienna.*
—Edward Lear
The Book of Nonsense

The old man of Vienna apparently found out what generations of herbal tea drinkers have discovered: that senna is a powerful laxative if taken in large amounts and that chamomile is a soothing relaxant that, among its many purported virtues, aids digestion.

Hopefully, though, the old man of Vienna was not allergic to ragweed. Because if he was, he might have had a reaction to chamomile tea—as did one 35-year-old American woman several years ago who went into anaphylactic shock after a few sips. Chamomile is a member of the same plant family as ragweed, asters and chrysanthemums, and people allergic to those plants had better be cautious of chamomile.

Herbal teas have been enjoyed for centuries throughout the world. But they have been the subject of controversy in the United States since their introduction into the mainstream marketplace two decades ago.

Comfrey, Lobelia and Sassafras

Comfrey tea has been implicated in liver disease, although only two such cases have been reported in the United States. In one instance, a 47-year-old woman developed a liver ailment after consuming up to 10 cups of comfrey tea a day and taking comfrey pills by the handful for more than a year in an attempt to cure her stomach pains, fatigue and allergies.

Although comfrey has enjoyed considerable popularity because of its supposed universal healing properties, there is reason to believe it is hazardous to health. Comfrey roots and leaves contain pyrrolizidine alkaloids, which have been found to cause cancer in rats. Celestial Seasonings, the industry leader in herb tea sales, dropped comfrey from its product line 10 years ago, and it was banned in Canada in 1989.

Lobelia tea can cause vomiting, breathing problems, convulsions, and even coma and death when used in large amounts. Lobelia, also called Indian tobacco, was used to treat asthma and bronchitis throughout the 19th century and experienced renewed popularity in the 1960s, when it was smoked by some young people to achieve a mild, legal “high.” It supposedly produced the same feelings of mental clarity, happiness, and

well-being when imbibed as tea.

In his book *The Honest Herbal*, pharmacognosist and former dean of the School of Pharmacy at Purdue University Varro E. Tyler says eating, drinking or smoking lobelia is “sheer folly.” “Lobelia is pretty toxic. It’s really not safe enough to use unless the dose is closely controlled,” he says.

The *Journal of the American Medical Association* recently reported the case of a 25-year-old woman who developed abnormal menstrual bleeding as a result of drinking large amounts of “seasonal tonic,” a homemade herbal brew. The woman was drinking the tea in an attempt to assuage her appetite so she could lose weight. The tea included a number of ingredients, three of which—tonka beans, melilot and woodruff—contain coumarin, an anticoagulant (blood thinner). The woman was also taking high doses of vitamins and other medicines that can intensify the effects of anticoagulants.

Aromatic sassafras tea, once popular as a stimulant and blood thinner and as a reputed cure for rheumatism and syphilis, causes cancer in rats when taken in large amounts. Oil of sassafras and safrole, major chemical components of the aromatic oil in sassafras root bark, were taken out of root beer more than 30 years



While there are few reported serious reactions to herbal teas, problems can occur, especially when teas are consumed in excess. Shown clockwise from above are: chamomile, which can be soothing but also may cause allergic reactions in persons sensitive to ragweed; comfrey, which may cause liver disease and which contains an alkaloid that causes cancer in rats; lemon grass, on which there is little safety data; sassafras bark, which causes cancer in rats and is banned from all foods; and raspberry leaves, for which the effects of consumption are unknown.



ago. And sassafras bark was banned from use in all food. Safrole-free extract, however, is allowed in food.

Nevertheless, herbal teas are a commercial success. They are purchased for their aroma and flavor and as a supposedly healthy alternative to caffeine beverages. Some are bought as home remedies for their alleged medicinal benefits.

Since the 1960s, when they experienced renewed popularity as part of the back-to-the-earth and natural foods movements, consumption of herbal teas has steadily increased. Today, a half dozen other herbal tea manufacturers share the shelf with more traditional teas made from orange and black pekoe at the supermarket. In fact, at least two pekoe tea manufacturers, Lipton's and Bigelow, have their own line of herbal teas.

Sales figures indicate consumers spent \$118.6 million last year on herbal teas at major supermarkets, up 9.8 percent from the previous year. This does not reflect herbal tea sales at smaller grocery stores and health food stores, for which figures are not available.

Safe or Unsafe?

But how safe is it to relax, prop your feet up, and sip a cup of tea containing, say, chamomile flowers, spearmint leaves, lemon grass, raspberry leaves, rosebuds, and orange blossoms?

Many herb experts would say that,

when consumed in reasonable amounts, major commercially packaged herbal teas are safe. They point out that, overall, there are very few serious reactions to herbal tea. Problems arise, they say, when teas are consumed in excess, when they are used for medicinal purposes, when an uninformed consumer mistakenly uses unsafe herbs, or when, as in the case of comfrey, a long-revered herb may be found to have toxic properties that were previously unknown.

"There are a lot of raw herbs available—everything from A to Z. And a lot of people are doing their own thing . . . buying herbs from natural foods stores and blending their own teas," says Angie Dorsey, a spokeswoman for Celestial Seasonings, which markets 20 herbal teas. "But most major herbal tea manufacturers are not using any dangerous herbs."

Celestial Seasonings, she said, brews teas for flavor and aroma, not for medicinal purposes. In selecting herbs, the company is guided by a list of 258 herbs and spices compiled by the Herb Research Foundation from regulations that FDA has published. "We avoid any herbs that are borderline or questionable in safety," she says.

To further insure the safety of its teas, the company tests its herbs for herbicides and pesticides and maintains an herbarium to check the identity of imported herbs. Because some safe herbs have

toxic look-alikes, it is easy to confuse one with another, Dorsey said.

Mark Blumenthal, executive director of the American Botanical Council, says that, in general, herbs that are sold as foods and teas have been used with relative safety for centuries.

"The idea that the herbs in your favorite tea may be toxic is, at the very least, misleading. If such everyday herbs were toxic, there would be a flood of poisoning cases among millions of herb users in this country alone. In fact, reports of adverse reactions to herbs are few." Blumenthal notes, however, that almost any substance can be toxic in large enough doses.

Caution Urged

The Food and Drug Administration takes a decidedly more cautious view of herbal teas.

"We don't know enough about herbal teas to conclude they are safe or to predict their effects in varying concentrations on the human body," says Sara Henry, a toxicologist in FDA's Center for Food Safety and Applied Nutrition. Although FDA has approved some herbs and spices for use in flavoring, very little is really known about many other herbs on the market, she says.

Henry says she cringes when she reads the ingredients on boxes of herbal tea at her local supermarket. "Raspberry leaf tea, for example," she says. "We know

absolutely nothing about the effects of consuming raspberry leaves. Caffeine has been extensively studied in animals, but nobody really knows anything about the safety of some of the herbs used in commercial herbal teas."

Henry said she is also concerned about the growing number of Oriental and Indian herbs on the market "because we don't know anything about them."

Sam Page, a natural products chemist in FDA's Center for Food Safety and Applied Nutrition, says most of the reported problems with toxicity in herbal teas have been associated with people who grow their own herbs.

"The problem is, most of these people don't have a long-term history of herbal use. Knowledge of herbs has not been passed down from generation to generation in their families, as it is in some other countries. So their experience with herbs is limited," says Page.

"Many of these herbal products are being consumed at much higher levels than the traditional uses. Many people are not cognizant of the basic premise of toxicology: 'The dose makes the poison.'"

Under these circumstances, he says, brewing your own tea "can be Russian roulette."

The case of an 85-year-old retired steelworker whose wife regularly concocted herbal teas from leaves found in their backyard illustrates Page's point. One day the man picked some leaves from an unfamiliar plant and made tea that had an unusually bitter taste. He drank one cup and within a few hours became gravely ill. Analysis of the tea leaves revealed that they belonged to the foxglove plant, from which the powerful heart drug digitalis is derived, and which can cause severe erratic heartbeat.

In another case, a 30-year-old woman died after drinking a tea she prepared from leaves of a tree she believed to be a eucalyptus. It wasn't. It was an oleander, which is poisonous.

Regulating Herbal Teas

FDA regulation of herbal teas falls into a somewhat gray area between food and drugs, according to Page. Depending on their intended use, herbs and other products, such as vitamins and diet aids, might sometimes be considered foods, sometimes drugs, and sometimes both.

FDA regards herbal teas that are consumed for their taste and aroma only (and not for medicinal purposes) as foods. Although there are no regulations governing herbal teas per se, any herb

that is considered safe by FDA for use in food is presumed to be safe in tea as well.

But for centuries, herbs and herbal teas have been used for medicinal purposes. Many of today's most potent medicines, such as digitalis, morphine and opium, are derived from herbs. If an herbal tea makes a claim to prevent or cure a disease, FDA considers it to be a drug and regulates it as such. This means the tea must be approved by FDA as safe and effective for its intended use.

Most major commercial herbal tea manufacturers avoid therapeutic claims or, if they do make them, skirt them gingerly with words such as "calming," "soothing," or "relaxing." However, some herbal tea manufacturers make therapeutic claims that are highly questionable.

One California company markets a smoker's tea to help people stop smoking, a weight-loss tea to "temporarily eliminate excess water weight," an herbal laxative tea, and a tea that supposedly relieves minor sore throats. It also sells teas for pregnancy, premenstrual syndrome, and teas designed to "tone" the body.

Other companies also make questionable claims. One markets a "dieter's tea" as "a low-cal food." Another markets a tea described as "the Brazilian way of losing weight without suffering." The same company sells a tea supposedly used by Indian tribes in their fertility rites and, by implication, designed to improve sexual potency. Still another sells a "therapeutic tea of the Incas" made from a tree used by the Incas for medicinal purposes.

No data has been submitted to FDA to substantiate any of these claims.

FDA takes action against herbs on a case-by-case basis when it has reason to question their safety—usually as a result of complaints or reports of serious reactions. The agency has received very few complaints about herbal teas in recent years.

"Keeping track of herbs is an impossible task," says FDA's Page. "The herb industry is the least organized of the food industries. Herbs are sold at a multitude of small outlets, and it's very difficult to find out who sells what and how much is being sold."

FDA Investigates

As a result of growing concern, FDA last spring directed its investigators to collect samples of a number of prod-

ucts—most of them herbal—sold in health food stores to determine which ones might be potential health hazards or which make unsubstantiated therapeutic claims.

Because of reported problems with comfrey tea, investigators collected samples of products made with comfrey to determine the levels of the potentially toxic pyrrolizidine alkaloids in them. Comfrey leaves and roots have been found to contain as many as nine such alkaloids, but the quantities vary widely among parts and species of the plant.

The herb industry itself is also trying to find out more about the safety of certain herbs. The Herb Research Foundation, at the request of the American Herbal Products Association, has initiated a program to evaluate 200 or so commercial herbs that are commonly available but not approved for use as food flavorings. Over the next 5 to 10 years, the foundation plans to gather information on each plant, including history of use in other countries, chemical composition, pharmacological properties, reports of adverse reactions, and toxicity studies. The foundation is planning to follow the same guidelines and often consults the same experts FDA would use to determine the safety of a food additive, according to Robert McCaleb, president of the foundation.

"We expect that the results will go both ways. We'll find herbs that are safe and herbs, probably like comfrey, that are not. And we'll also find plants where conclusions are harder to draw," says McCaleb.

In 1984, faced with similar questions about herb safety, Canada established an advisory committee to review the available information on herbs and make recommendations. As a result, Canada banned the sale of some 57 herbs and required warning labels on five others that, though generally not considered harmful, could pose a health risk if used during pregnancy.

For American herbal tea drinkers, though, it might be best to play safe and heed the old proverb about those who gather wild mushrooms: "There are old mushroom hunters. And there are bold mushroom hunters. But there are no old, bold mushroom hunters." ■

Sharon Snider is a member of FDA's public affairs staff.

How to Take Your Medicine

Angiotensin-Converting Enzyme Inhibitors

How you take a drug can affect how well it works and how safe it will be for you. 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 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 10th installment of this series features a class of drugs called angiotensin-converting enzyme inhibitors.

Conditions These Drugs Treat

All angiotensin-converting enzyme (ACE) inhibitors are used to treat high blood pressure. In addition, captopril and enalapril are used to treat heart failure, usually only after other medications, such as digitalis, have been tried. ACE inhibitors can be used for other conditions as determined by your doctor.

How to Take

Captopril should be taken on an empty stomach one hour before meals. All other ACE inhibitors can be taken without regard to meals.

ACE inhibitors are potent medicines that treat but do not cure chronic conditions such as high blood pressure. That is why it is important to take the ACE inhibitor regularly and make sure you're taking the right amount. Taking doses at the same time each day will help you remember to take the drug regularly. Con-

Common Names

captopril (Capoten)

enalapril (Vasotec)

lisinopril (Prinivil, Zestril)

ramipril (Altace)

tinue any diet and exercise program prescribed by your doctor.

Missed Doses

If you miss a dose, take it as soon as you remember. As a rough guideline, estimate the number of hours between when you should have taken your missed dose and when your next dose is scheduled (if you take it twice a day, for instance, the time between doses is 12 hours). If you have passed the halfway point (which is six hours in this example), do not take the missed dose. Instead, continue with your next regularly scheduled dose. Do not take two doses at the same time.

Relief of Symptoms

ACE inhibitors begin to work immediately after the first dose. However, a few weeks may be needed before the full effects occur. The dosage of the ACE inhibitor may need to be adjusted by your doctor when you first begin taking it.

Side Effects and Risks

Fatigue, dizziness, headache, insomnia, nausea, vomiting, and diarrhea are all common side effects. These are all usually mild.

Loss of the taste sense can occur, especially with captopril. Taste usually returns within two to three months, even if you are still on the medication. Sometimes slight weight loss can accompany the loss of taste.

Some people develop a persistent dry cough while taking ACE inhibitors. The cough usually does not go away unless the medication is stopped. If this side effect occurs and is bothersome, you should discuss it with your doctor.

ACE inhibitors can cause dizziness, lightheadedness, or even fainting, usually during the first few days. These effects are due to lowered blood pressure and occur mostly when getting up from a sitting or prone position. Consult your doctor if these symptoms persist, especially if fainting occurs. Sometimes changes in the dosage of the ACE inhibitor or other medications can ease these symptoms.

A mild, sometimes itchy, skin rash can occur and may be accompanied by fever or joint pains. This usually happens within the first four weeks of beginning an ACE inhibitor, especially captopril. Consult your doctor if this occurs since

dosage changes or other medications can help clear the rash.

More serious but infrequent reactions that sometimes occur with ACE inhibitors are:

- *Fever and chills.* Although rare, ACE inhibitors (mostly captopril) can cause a decrease in certain white blood cells, increasing susceptibility to infections. Common symptoms include fever, chills, sore throat, and mouth sores. If these symptoms occur, contact your doctor immediately. The lowered cell count is usually reversible.
- *Allergic reaction.* This is evidenced by sudden difficulty in swallowing or breathing; hoarseness; flushed or pale complexion; and swelling of the face, mouth, hands, or feet. Stop taking the medication immediately, and call your doctor or seek emergency help if the symptoms are severe.

- *Chest (heart-related) pain, rapid or pounding heartbeat.* These symptoms tend to occur most often when you first start taking an ACE inhibitor.

If these serious reactions or other new symptoms occur, contact your doctor immediately.

Precautions and Warnings

Do not stop taking an ACE inhibitor on your own.

ACE inhibitors can sometimes cause a reversible decrease in kidney function. Your doctor may periodically check your kidney function by either blood or urine tests while you are on the medication. If you notice your feet or ankles swelling or weight gain, notify your doctor.

Exercising in hot weather, excessive perspiration, vomiting, or diarrhea can lead to loss of fluid (dehydration) and intensify the ability of ACE inhibitors to

lower blood pressure. Low blood pressure could lead to severe dizziness or even fainting. Consult your physician if any of these conditions occurs.

ACE inhibitors can occasionally cause the body to retain too much potassium. Rarely, potassium excess in the body can cause confusion, irregular heartbeat, weakness in the legs, nervousness, or tingling in the hands, feet or lips. If any of these occurs, contact your doctor immediately. Also, consult your doctor before using any salt substitutes, since many of these contain potassium.

Diabetic patients who test their urine for acetone should be aware that captopril can cause a false-positive reading.

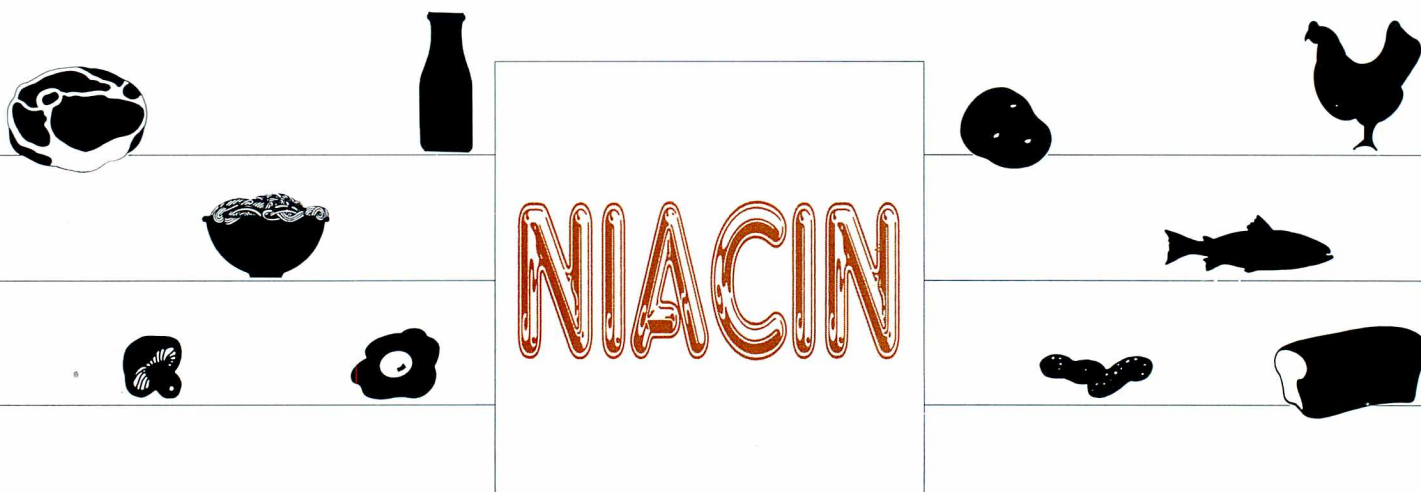
Animal studies show ACE inhibitors may cause problems during pregnancy. In a few human reports, some babies of mothers taking ACE inhibitors have been born with very low blood pressure. Let your doctor know if you are or intend to become pregnant while on an ACE

inhibitor.

Captopril is secreted into breast milk. It is not known if either enalapril or lisinopril gets into breast milk. In general, breast-feeding is not recommended while taking these drugs unless directed by a doctor. ■

—Igor Cerny





U.S. Recommended Daily Allowances

Infants (0–12 mo.)	Children (1–3 years)	Adults and Children 4 Years +	Pregnant or Nursing Women
8 mg	9 mg	20 mg	20 mg

(The U.S. RDA amounts are sufficient to meet the needs of practically all healthy people.)

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

Niacin (nicotinic acid, nicotinamide) is a water-soluble vitamin whose requirement is partly met by conversion in the body of the essential amino acid tryptophan to niacin.

Functions: Involved in carbohydrate, protein and fat metabolism.

Sources: Enriched cereal-grain products; meat, fish, poultry, cheese, eggs, and milk because they contain tryptophan; peanuts; mushrooms; potatoes.

Deficiency: Severe niacin deficiency causes pellagra, a disease characterized by mouth sores, skin rashes, diarrhea, and

dementia. Deficiency is rarely seen in the United States, though, because most people have adequate intakes.

Excess: Large amounts of niacin, when taken in the nicotinic acid form of the vitamin, act as a drug. Nicotinic acid is often prescribed as a cholesterol-lowering drug, and should be taken only under the supervision of a physician. Side effects include vascular dilation of the skin (flushing) and gastrointestinal distress. Prolonged intake may cause liver damage.

Nicotinamide is not known to act as a drug. Effects of high doses are unknown. ■

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.

■ **Migration of food additives** is the subject of a new research report FDA is making available to the public. Titled "High Temperature Migration of Indirect Food Additives to Foods," the study was conducted to suggest ways to improve FDA's procedures for evaluating migration of indirect food additives from food packaging. Copies of the report may be ordered from the National Technical Information Service (NTIS), U.S. Department of Commerce, 5285 Port Royal Road, Springfield, Va. 22161. Orders must reference NTIS number PB 91-127-209 and include payment of \$31 for each copy. Payment may be made by check, money order, charge card (American Express, Visa or MasterCard), or billing arrangements made with NTIS. For further information, contact NTIS at (703) 487-4650. (FR Feb. 27)

■ **Proposed guidelines about genetically engineered organisms** were formulated by the U.S. Department of Agriculture's office of biotechnology. For additional information, contact Marilyn Cordle, Room 324-A, Administration Building, 14th St. and Independence Ave., S.W., Washington, D.C. 20250-2200; telephone (703) 235-4414. (FR Feb. 1)

In a related move, the Animal and Plant Health Inspection Service (APHIS) announced that 18 applications for permits to release genetically engineered organisms into the environment are being reviewed. For further information, contact Mary Petrie, Biotechnology, Biologics and Environmental Protection, Biotechnology Permits, APHIS, U.S. Department of Agriculture, Room 844, Federal Building, 6505 Belcrest Road, Hyattsville, Md. 20782; telephone (301) 436-7612. (FR Feb. 28)

■ **Controlling *Salmonella enteritidis*** spread among commercial egg-producing chickens is the subject of regulations developed by the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture. For further information, call (301) 436-5777. (FR Jan. 30)

■ **Modifications to drug Good Manufacturing Practices** have been proposed that will allow manufacturers more flexibility in producing animal and human drugs without sacrificing product quality. For more information, contact Dockets Management Branch, HFA-304, FDA, Room 4-62, 5600 Fishers Lane, Rockville, Md. 20857. (FR Feb. 12)

■ **Establishment of a bone marrow registry** is under consideration at the National Heart, Lung, and Blood In-

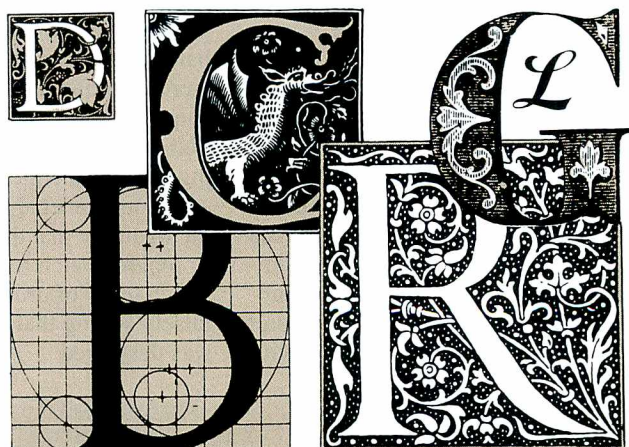
stitute of the National Institutes of Health. Issues to be addressed include establishing and enforcing criteria and standards. For further information, contact Paul McCurdy, M.D., division of blood diseases and resources, NHLBI, Room 516, Federal Building, 7550 Wisconsin Ave., Bethesda, Md. 20892; telephone (301) 496-8387. (FR Feb. 7)

■ **Veterinary biological product** manufacture and distribution will be discussed at a public meeting on Aug. 15 and 16, 1991, in Ames, Iowa. Standardization of international regulations and safety issues will also be discussed. For additional information, contact Dr. Frank Tang, Biotechnology Coordination and Technical Assistance Staff, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Room 851, 6505 Belcrest Road, Hyattsville, Md. 20782; telephone (301) 436-4833. (FR Feb. 20)

■ **Preparation of investigational new drugs** for humans and animals are addressed in guidelines available from FDA. Write: CDER Executive Secretariat Staff (HFD-8), Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, Md. 20857. (FR Feb. 21)

■ **A cumulative list of designated orphan products** is now available to the public from FDA. Contact the Dockets Management Branch (HFA-305), FDA, Room 4-62, 5600 Fishers Lane, Rockville, Md. 20857, or the National Information Center for Orphan Drugs and Rare Diseases, P.O. Box 1133, Washington, D.C. 20013-1133. (FR Feb. 27)

■ **Responding to a petition** filed by Pharmacists Planning Service, Inc., FDA will accept comments on print size and style for over-the-counter drug labeling, particularly as it affects those with impaired vision. The deadline for comments is June 4, 1991. Write to Dockets Management Branch (HFA-305), FDA, Room 4-62, 5600 Fishers Lane, Rockville, Md. 20857. Refer to docket number 90P-0201. (FR March 6)



tripennamine HCl · Selenium E · furosemide · Milk Fever Single · Milk Fever Double · Selenium-
Vit-E · Hy-Phos · methandriol dipropionate · Cal-Phos Suspe · Lidocaine · Hy-Energy · Cal-
Ereat-I.M. · Multi-B Super · K3 · triplennamine HCl · Selenium E · furosemide · Milk Fever Single
· Milk Fever Double · Selenium-Vit-E · Hy-Phos · methandriol dipropionate · Cal-Phos
Suspension · Hy-Energy · Cal-Ereat-I.M. · Multi-B Super · K3 · triplennamine HCl · Selenium
E · furosemide · Milk Fever Single · Milk Fever Double · Selenium-Vit-E · Hy-Phos · methandriol
· Selenium E · furosemide · Milk Fever Single · Milk Fever Double · Selenium-Vit-E · Hy-Phos ·
methandriol dipropionate · Cal-Phos Suspension · Lidocaine · Hy-Energy · Cal-Ereat-I.M. ·
Multi-B Super · K3 · triplennamine HCl · Selenium E · furosemide · Milk Fever Single · Milk
Fever Double · Selenium-Vit-E · Hy-Phos · methandriol dipropionate · Cal-Phos Suspension ·
Lidocaine · Hy-Energy · Cal-Ereat-I.M. · Multi-B Super · K3 · triplennamine HCl · Selenium E ·
furosemide · Milk Fever Single · Milk Fever Double · Selenium-Vit-E · Hy-Phos · methandriol dipropionate

Veterinarian Convicted in Illegal Drug Scheme

In the first case investigated by FDA's National Animal Investigation Team to go to jury trial, a federal jury recently convicted an Iowa veterinarian of four felony counts involving receiving and distributing illegal animal drugs. To date, 40 individuals and corporations have been found guilty as part of the animal investigation team intensive crackdown on illegal sales of animal drugs.

John A. Minneman, D.V.M., of Washington, Iowa, was found guilty of one count of conspiracy and three counts of receiving and distributing the drug chloramphenicol, which is banned in the United States for use in food-producing animals. Although an extremely effective antibiotic, chloramphenicol can cause a fatal blood disorder called aplastic anemia in humans. Even indirect exposure, such as eating meat tainted with residues of the drug, is potentially deadly.

An anonymous phone call to an investigator in FDA's Des Moines, Iowa, office led to important evidence, including samples of the chloramphenicol used by Minneman to treat cattle at the farms of several clients.

Among the information collected by FDA was evidence that the chloramphenicol was purchased from Andrew J. Cotten, D.V.M. Cotten, as part of a plea agreement, pleaded guilty to two felony charges just before his trial, which was scheduled for November 1990. (For more information on the case against Cotten, see "Veterinarian Indicted" in the November 1990 *FDA Consumer*.)

Cotten testified at Minneman's trial that, in an effort to avoid suspicion, Minneman told Cotten to label the chloramphenicol "Spec II" and address the packages to Minneman's daughter rather than the veterinary clinic. Cotten further testified that Minneman said he needed to hide the chloramphenicol from clinic employees, especially his partner, who had complained about Minneman's illegal use of the drug.

The trial in the U.S. District Court for the Northern District of Iowa began on

Jan. 7, 1991. Two days later, the jury found Minneman guilty on all four felony charges. The conspiracy conviction carries a maximum sentence of five years in prison and a fine of up to \$250,000. Each count relating to receipt and distribution of illegal animal drugs carries a maximum sentence of three years in prison and a fine of up to \$250,000.

At press time, the court had not set a date for sentencing.

Bakery Complies After Shutdown

A Philadelphia baking company with a history of insect and rodent infestation was found in contempt of court last October after it failed to comply with FDA's request to cease operations.

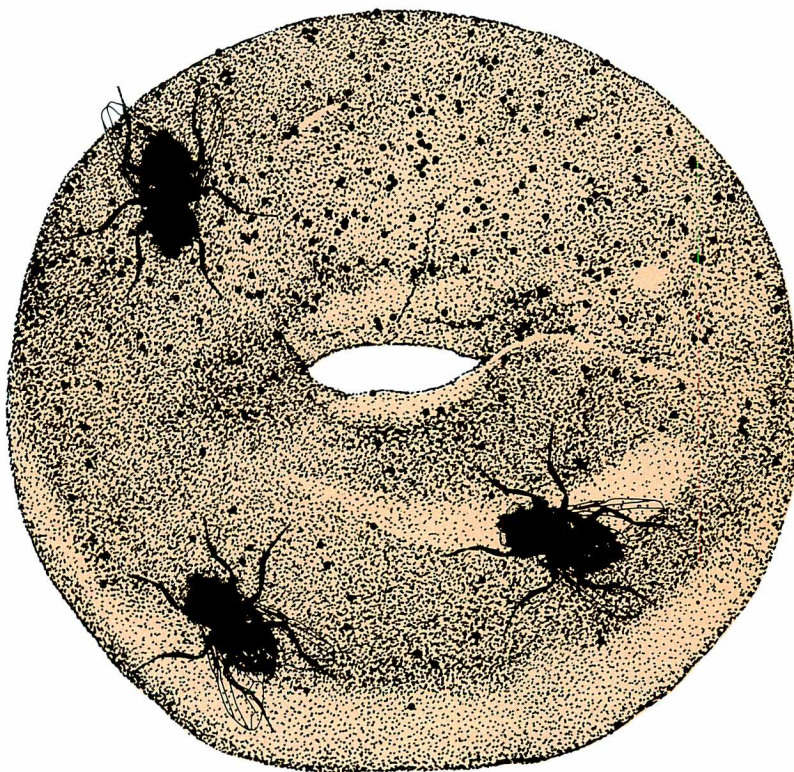
The U.S. District Court for the Eastern District of Pennsylvania found Tally-Ann Baking Co. and its president, Domenic Mastrangelo, in civil contempt for failing to comply with an earlier court order that required the firm to operate under sanitary conditions. On Oct.

26, 1990, the court ordered the bakery to suspend operations immediately and imposed a fine of \$10,000 for each day it remained in operation.

The company, which makes bread, rolls, bagels, and bread crumbs, remained shut down for nearly six weeks before FDA approved its reopening.

The recent court actions stem from evidence FDA collected between 1985 and 1990 showing that the bakery repeatedly failed to get rid of insects and rodents despite numerous warnings from FDA. Indeed, in 1985, the company and its president were convicted of eight counts of manufacturing bakery products in an insect- and rodent-infested environment and shipping the products in interstate commerce. They were given a suspended sentence, fined \$8,000, and placed on three years' probation.

During the probationary period, FDA conducted four inspections, each of which revealed insect and rodent infestation, as well as other insanitary conditions. A list of violations was presented to Mastrangelo following each inspection.



tion. In addition, FDA issued two notices of adverse findings to Mastrangelo, who responded that he would correct the problems.

Following the fourth inspection in October 1987, FDA informed the district court of Mastrangelo's failure to adhere to the terms of probation. The court, in turn, asked FDA to submit an injunction order explaining why the bakery should be restrained from further operations until corrections were made.

The injunction was filed in November 1988, but later dismissed by the court. Instead, the court extended Mastrangelo's probation one year and ordered a court-appointed pest control consultant to inspect the firm twice a month.

However, subsequent inspections by FDA in September 1989, January 1990, and September 1990 revealed ongoing insect and rodent infestation. As a result, FDA submitted another injunction recommendation. The evidence included:

- various live and dead insects—including beetles and flies—in baking equipment

- live insects on bags of yellow cornmeal
- rodent urine and rodent hair on the outside of cornmeal bags
- one live rodent and numerous rodent pellets on the premises
- cockroaches on the premises
- numerous flies landing on finished products, food contact surfaces, and baking equipment
- live insects, insect larvae, and insect fragments in finished products.

On Oct. 2, 1990, the U.S. attorney's office filed for permanent injunction. On Oct. 16, District Judge James Kelly entered a consent order permanently enjoining Tally-Ann Baking and Mastrangelo from receiving, manufacturing or shipping any food until FDA found the bakery to be in sanitary condition. In particular, the court ordered Tally-Ann Baking to eliminate insect infestation and close entry routes for insects and rodents, thoroughly clean the bakery and all equipment, and establish a detailed written sanitation control program.

FDA inspected the bakery on Oct. 16 and 18. Both times, it determined that the

firm was not in compliance with the consent order and notified the company and Mastrangelo to cease operations. Both times, they refused.

As a result, on Oct. 26, the court held the company and Mastrangelo in contempt and ordered the bakery to close.

Tally-Ann reopened Nov. 30, after an FDA inspection revealed the firm was in compliance with the consent order and operating in a sanitary condition. FDA plans to conduct follow-up inspections to ensure that the company continues to operate in compliance with the consent order.

Flowering Fern Refused Entry to U.S.

A routine import inspection by FDA Chicago district inspector Ruben De La Garza turned up a very non-routine food product. Pouches of Boiled Flowering Fern, an edible plant sold to Oriental groceries, were denied entry into the country because tests showed the product to be a potential health hazard.

On Aug. 10, 1990, FDA Inspector De La Garza collected a sample of the fern product, shipped from the Japanese manufacturer Yugen Kaisha Yamamoto Shoji to the U.S. importer Chicago Food Corp. in Chicago, Ill. Analysis by Chicago district chemist Theodore Piwowar showed that the pH level, water activity, and other factors classified the product as a low-acid canned food.

Because low-acid canned foods sometimes harbor the *Clostridium botulinum* organism that, in an anerobic environment, produces the toxin that causes botulism, all such products must be processed using temperatures high enough to destroy any *botulinum* spores. FDA inspectors were unable to determine whether or not the pouches of flowering fern had been processed properly because the manufacturer was not registered with FDA, nor was its process filed as required by the agency. FDA compliance officer Russell W. Gripp notified the firm that its product had been detained. The company responded with the packaging process, saying that the flow-

ering fern had been pickled in soy sauce or seasoned juice, then washed. Water and a 15 percent salt solution were added, and the fern was boiled. The flowering fern in solution was then placed in pouches and sealed. The company argued that a 15 percent salt solution was sufficient to preserve the flowering fern.

FDA maintained, however, that, because it had not undergone heat processing, the flowering fern would have to have been packaged initially in at least a 17 percent salt solution to prevent production of *Clostridium botulinum* toxin. Chicago Food Corporation proposed to recondition the flowering fern to increase its salt content. FDA refused the proposal because the product had not been manufactured in such a way as to guard against production of the *botulinum* toxin, and the company offered only to change the salt content of the pouches rather than reconstitute using heat disinfection. The shipment was refused entry and subsequently destroyed by the firm on Dec. 3, 1990.

On Jan. 30, 1991, based on a written recommendation by Gripp, FDA's Import Operations Branch issued an import bulletin recommending that all field offices increase surveillance sampling of all pouched products manufactured by Yugen Kaisha Yamamoto Shoji and submit collected samples for laboratory analysis.

—This small sample of reports from the field was prepared by Jessica Auerbach, Paula Kurtzweil, and Dori Stehlin.



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/Contamination, Spoilage, Insanitary Handling

PRODUCT: **Bread product**, at Minneapolis, Dist. Minn.; Civil No. 4-90-244.

CHARGED 4-3-90: When imported, the article (labeled "Crispbread Lite Rye . . . Made by Wasa GmbH, West Germany, for Sandoz Nutrition Corporation, Minneapolis, MN") contained rodent and other animal filth—402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65855; S. No. 90-530-085; S.J. No. 1)

PRODUCT: **Margarine and frozen ready-to-bake fruit pies**, at Montgomery, M. Dist. Ala.; Civil No. 90-T-555-N.

CHARGED 5-24-90: While held for sale, the articles were unfit for food because they possessed an ammoniacal odor due to an ammonia leak into the storage cooler and freezer—402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65865; S. No. 90-574-091 et al.; S.J. No. 2)

PRODUCT: **Rice**, at Brooklyn, E. Dist. N.Y.; Civil No. 90-0976.

CHARGED 3-20-90: While held by Hank Lee & Co., Inc., Brooklyn, N.Y., the article contained rodent filth and had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65826; S. No. 90-546-748 et al.; S.J. No. 3)

Food/Economic and Labeling Violations

PRODUCT: **Shrimp, frozen**, at Lubbock, N. Dist. Texas; Civil No. CA5-90-0072W.

CHARGED 3-29-90: When shipped by R & G Enterprises (Al Copeland Enterprises, Inc.), Jefferson, La., the article labeled "Keep Frozen . . . Pearl Brand Shrimp Packed By Indian Ridge Shrimp Co. Houma, La." consisted in part of water that had been added to increase the article's weight—402(b)(4).

DISPOSITION: Consent—authorized release to the shipper for bringing into compliance. (F.D.C. No. 65851; S. No. 90-527-509; S.J. No. 4)

PRODUCT: **Tapioca-snack mix, shrimp crackers, dried shrimp paste, and other food stocks**, at Paramount, C. Dist. Calif.; Civil No. 90-0154TJH(Ex).

CHARGED 1-10-90: When imported from Indonesia, the tapioca-snack mix contained the nonconforming color additive FD&C Yellow No. 5 (nonconforming since the presence of FD&C Yellow No. 5 was not specifically declared on the label), and the labeling of the tapioca-snack mix failed to declare the presence of the artificial colorings FD&C Red No. 5, FD&C Blue No. 1, and FD&C Yellow No. 5—402(c), 403(k); the shrimp crackers contained insect filth; and the shrimp paste contained rodent filth—402(a)(3); and all of the articles had been held under insanitary conditions—402(a)(4).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65801; S. No. 90-615-241 et al.; S.J. No. 5)

Drugs/Human Use

PRODUCT: **Cafegot P-B tablets (a pentobarbital-belladonna-caffeine-ergotamine combination)**, at Peabody, Dist. Mass.; Civil No. 89-1287-WF.

CHARGED 6-13-89: When shipped by Sandoz Pharmaceuticals Corp., Inc., East Hanover, N.J., the article was a new drug without an effective approved New Drug Application—505(a).

DISPOSITION: The article was claimed by the shipper, who denied the charge, demanded trial by jury, and also asserted that the article was not a new drug and was exempted under the grandfather clause of PL 87-781. The government served a request for admissions on the claimant. When the claimant had not answered such request after more than 30 days, the government moved for summary judgment. The claimant moved to strike the government's motion as being premature and based on an incorrect interpretation of the discovery deadline set forth in the scheduling order of the court. Shortly thereafter the claimant ceased all manufacture and distribution of the article and advised customers of the article's discontinuance. Ultimately, a consent decree of condemnation ordered the article destroyed. (F.D.C. No. 65671; S. No. 89-564-502; S.J. No. 6)

PRODUCT: **Fiorinal With Codeine No. 1 capsules and Fiorinal With Codeine No. 2 capsules (butalbital-caffeine-aspirin combinations, with 7.5 mg and 15 mg respectively of codeine-phosphate)**, at East Hanover, Dist. N.J.; Civil Nos. 86-3877DRD and (upon appeal) 88-5481.

CHARGED 10-3-86 and amended 3-8-88 to add a complaint for injunction: While held by Sandoz Pharmaceuticals Corp., E. Hanover, N.J., the labeling of the articles lacked adequate directions for use, and the articles were not exempt due to their new drug status—502(f)(1); and the articles were new drugs without effective approved New Drug Applications—505(a).

DISPOSITION: *District Court*—The articles were claimed by the possessor-manufacturer, who denied the charges, demanded trial by a jury, and also asserted that the proceeding must be dismissed because there was no determination that the articles were new drugs. Subsequently, the claimant moved to stay the proceedings

pending resolution of a companion case in the Southern District of Ohio, and the government moved for summary judgment. The government opposed the claimant's motion for a stay, as being unjustified and prejudicial to the public. Meanwhile, the claimant moved for discovery and for a remand to FDA. After a hearing on the claimant's motion for a stay, the court denied the motion for a stay and ordered that the claimant respond to the government's motion for summary judgment.

After additional litigation, the government moved to amend the complaint to enjoin the claimant from further interstate shipment of the seized articles until the claimant had obtained proper statutory authority to market such drugs. In the claimant's answer to the amended complaint, the claimant continued to defend on the basis of an absence of an administrative record, and in addition the claimant asserted that this action deviated from actions taken or not taken under similar circumstances and as such was discriminatory and an abuse of discretion.

The government asserted that the only contested issue was whether the articles were new drugs. The claimant submitted declarations supporting its contentions that the articles were not new drugs and moved for a continuance to permit discovery to oppose the government's motion for summary judgment.

After evaluating the documentary evidence submitted by the parties, the court granted summary judgment to the government. The court noted the following: that Sandoz's Fiorinal products (Fiorinal and Fiorinal With Codeine (FWC) Nos. 1, 2 & 3) were drugs that originally contained aspirin, phenacetin, caffeine, and butalbital; that, pursuant to an FDA directive in 1983, the phenacetin had been removed and the quantity of aspirin had been increased; that the original FWC Nos. 1, 2 & 3 had had an informal FDA written opinion that such original formula FWC products were not new drugs, but that such opinion (and all other informal FDA opinions) had been revoked in 1968; that in 1973 Sandoz had submitted data to support its NDA for its new formulation of Fiorinal (but not for any of the new FWC formulations) and FDA had published a notice stating that Fiorinal had "been evaluated as effective for . . . tension . . . headache"; that Sandoz had subsequently filed abbreviated New Drug Applications (NDAs) for its FWC products, which FDA had rejected; that in 1978 FDA had informed Sandoz that the FWC products were new drugs requiring full NDAs and had advised that studies of FWC No. 1 would probably *not show effectiveness*; that, after further correspondence, Sandoz had submitted a third request that FDA accept an abbreviated NDA for FWC products; and that, after a preliminary review of the abbreviated NDA for the FWC products, FDA had indicated that such abbreviated NDA was not approvable.

The district court reviewed six published clinical studies of Fiorinal products, *i.e.*, the following: A) a study of the previous formulation of FWC No. 3 containing phenacetin and 30 mg of codeine; B) a study of the previous formulation of FWC No. 2 containing phenacetin and 16 mg of codeine; C) a study of FWC No. 3 with 30 mg of codeine that did not measure any statistical significance in analgesic efficacy over the compared product; D) a study involving the current formula for FWC No. 2 with 15 mg of codeine and a similar analgesic combination with codeine that

found no statistically significant differences between the active medications; E) a study of the earlier FWC No. 3 with phenacetin and 30 mg of codeine; and F) a study comparing the original Fiorinal (containing phenacetin) and the original FWC No. 3 (containing phenacetin and codeine).

The court found the following: that Sandoz must show that each ingredient in FWC No. 1 and FWC No. 2 contributed to the claimed effects; that there was an absence of published clinical data to show that 7.5 mg of codeine would contribute to the effects claimed for FWC No. 1; that studies conducted using the old formulation of FWC products were not well-controlled clinical investigations of products using the new formulation; and that extrapolation of the data derived from them was not justified for the purpose of a "new drug" determination. The court concluded that the proper rule was that the combination policy of 21 *C.F.R.* 300.50 can only be met by studies of the particular drug product at issue or a drug having the same active ingredients which are demonstrably bioequivalent.

In addition, the court rejected Sandoz's contention that the case should be remanded to FDA and denied Sandoz's motion for a continuance and for discovery. Since formal application for an injunction had not been made, the court did not act on that request, although the court stated that FDA might make formal application for an injunction if it wished to do so.

Subsequently, in response to the government's request for an injunction, the court issued an order requiring Sandoz to show cause why it should not be enjoined from shipping FWC Nos. 1 & 2. However, in light of Sandoz's assurances of the discontinuance of FWC Nos. 1 & 2, the government withdrew its request for an injunction.

Sandoz ceased to market FWC Nos. 1 & 2; but Sandoz filed a notice of appeal. Meanwhile, Sandoz had litigated a similar seizure of FWC No. 3 in the Southern District of Ohio (see S.J. No. 8 of this issue of *FDA Consumer*); and, based on the collateral estoppel effect of the judgment in this seizure of FWC Nos. 1 & 2 in New Jersey, the district court for the Southern District of Ohio had condemned FWC No. 3.

Court of Appeals for Third Circuit—Sandoz and the government filed a joint motion to stay the proceedings in this action, advising the court as follows: that Sandoz would not resume marketing of FWC Nos. 1 & 2 unless FDA approved such products or unless the district court's opinion was reversed; that Sandoz's primary interest was to overturn the judgment against FWC No. 3 in the Southern District of Ohio; that Sandoz had submitted an NDA for FWC No. 3 and, if FDA approved of such NDA, Sandoz would not pursue its appeal; that FDA believed that it could determine whether the FWC No. 3 NDA was approvable within the period of the stay; and that a stay might conserve judicial resources and avoid needless litigation. The Court of Appeals granted the requested stay.

Subsequently, the appeal was pursued by Sandoz, which argued that it could show general recognition of FWC Nos. 1 & 2 through extrapolation from data derived from tests of other products. However, the Court of Appeals expressly affirmed the district court's reasoning and its conclusion that 21 *C.F.R.* 300.50 re-

quired manufacturers to submit evidence establishing the contribution of each ingredient to the effectiveness of a product for its indicated applications. The Court of Appeals also held that the district court did not err in concluding that “studies conducted using the old formulation are not well-controlled clinical investigations of products using the new formulation and extrapolation of the data derived from them is not justified for the purpose of a ‘new drug’ determination”.

The Court of Appeals also ruled against Sandoz on its claim for a “flexible” approach to proof required for general recognition of a drug, and against Sandoz’s argument that summary judgment was improper because the district court had resolved a disagreement between the Sandoz and FDA expert witnesses as to the effectiveness of FWC products. In addition, the Court of Appeals also rejected Sandoz’s argument that Sandoz should have been permitted discovery; such evidence being, as the district court concluded, immaterial as a matter of law. Accordingly, the judgment of the district court for the government was affirmed. (F.D.C. No. 65032; S. No. 86-426-500; S.J. No. 7)

PRODUCT: Fiorinal With Codeine No. 3 capsules (butalbital-caffeine-aspirin combination with codeine phosphate), at Columbus, S. Dist. Ohio; Civil Nos. C-2-86-741 (on appeal) 88-3691 and (petition for certiorari) 89-1648.

CHARGED 6-17-86 and amended 5-24-88 to add a complaint for an injunction: When shipped by Sandoz Pharmaceuticals Corp., East Hanover, N.J., the article was a new drug without an effective approved New Drug Application—505(a).

DISPOSITION: District Court—The article was claimed by the shipper (Sandoz), who denied the charge. Sandoz moved to refer the case to FDA for administrative hearings on the issue of whether the article was a new drug. The government opposed such motion and moved for summary judgment. Sandoz opposed the government’s motion for summary judgment, submitting six clinical studies involving various formulations of Fiorinal products, in order to show that the seized product was not a new drug. Meanwhile, in the District of New Jersey, the government brought a seizure action against Fiorinal With Codeine Nos. 1 & 2 capsules (drugs having the same formula as Fiorinal With Codeine No. 3 (FWC No. 3) but with 30 mg of codeine instead of the 7.5 mg and 15 mg in FWC Nos. 1 & 2 respectively). See S.J. No. 7 of this issue of *FDA Consumer*.

Subsequently, the government moved to amend the complaint for forfeiture to request an injunction, relying on a favorable ruling in the New Jersey seizure action. In addition, the government filed a motion for judgment, contending that the principles of collateral estoppel barred Sandoz from relitigating the new drug issue and the issue of an administrative hearing and that judgment should be granted the government in this action.

Relying on the judgment in the District of New Jersey action, the court found that Sandoz was collaterally estopped and awarded summary judgment to the government. The court also granted the government’s motion to amend the complaint to include injunctive relief. Sandoz had argued that the New Jersey court did not decide the same issues because the FWC product in this case

differed from the FWC product in the New Jersey case. However, the court noted the following: that the FWC products contained the same ingredients; that the only difference in the products was the amount of codeine; that, in the New Jersey action, the general recognition of effectiveness of the FWC Nos. 1 & 2 products had not been demonstrated through adequate and well-controlled investigations; that Sandoz could not rely on the older clinical studies conducted on the original formula FWC products or with other preparations, since bioequivalency between the present FWC products and the studied substances had not been demonstrated; that the lack of any study of the effectiveness of the 40 milligrams of caffeine applied to all the FWC products; and that the legal issues (especially those concerning the non-codeine components of Fiorinal) were exactly the same.

The district court also found that Sandoz had had a full and fair opportunity to litigate the issue in the New Jersey action. Accordingly, summary judgment was awarded to the government, and the motion to amend was granted. The district court took note of the parties’ agreement on injunction relief in the New Jersey action and sought further briefing on injunctive relief in this action. Subsequently, the district court, in its award of judgment to the government, ordered the destruction of the seized FWC No. 3, and ordered that Sandoz be enjoined from further distribution of FWC No. 3, but stayed its order while Sandoz appealed.

Court of Appeals for the Sixth Circuit—Upon appeal, Sandoz argued that the different amounts of codeine in the FWC products required different determinations and that the New Jersey action involved an unmixed question of law. However, the Court of Appeals determined that both seizure actions required identical showings that each ingredient contributed to the claimed effect, that Sandoz had defended its products’ efficacy with the same six studies and declarations of experts, and that Sandoz had failed to show the contributions of the non-codeine components. Accordingly, the Court of Appeals found that collateral estoppel was permissible in this case because the New Jersey judgment was a mixed question of fact and law in an action very similar to this case. The Court of Appeals also ruled against a number of other Sandoz arguments, stating that Sandoz could not argue that the New Jersey court’s findings on all six studies were unnecessary when Sandoz had placed all six studies into evidence, that Sandoz failed to show that discovery could have led to a different result in either seizure action, that Sandoz had a full and fair opportunity to litigate in the New Jersey action, that Sandoz had ample incentive to litigate both actions vigorously (i.e., sales of over 3 million dollars a year of FWC Nos. 1 & 2, and more of FWC No. 3), and that Sandoz’s Bentex claim failed because the New Jersey court had fully examined such claim before rejecting it. Since the Court of Appeals affirmed the district court’s judgment for the government, Sandoz petitioned for certiorari. The petition was denied. (F.D.C. No. 64672; S. No. 85-483-204 et al.; S.J. No. 8)

Medical Devices

PRODUCT: Condoms, Itasca, N. Dist. Ill.; Civil No. 89 C 8770. **CHARGED** 11-27-89: The quality of the articles, which had been

shipped from Newark, N.J., fell below the articles' purported quality, because the articles contained holes—501(c) and the articles' labeling contained false and misleading claims for the prevention of disease when the articles contained holes—502(a). DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65788; S. No. 90-577-470 et al.; S.J. No. 9)

PRODUCT: **Gloves, latex, for medical examination**, at Indianapolis, S. Dist. Ind.; Civil No. IP90-425C. CHARGED 4-4-90: The quality of the article, which was labeled "Latex Examination Gloves . . . Hua Shu-Yee Industrial Co., Ltd. . . . Made In Taiwan," fell below the article's purported quality due to excessive holes—501(c); and the article's label lacked the place of business of the manufacturer—502(b)(1). DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65849; S. No. 90-456-995; S.J. No. 10)

PRODUCT: **Gloves, latex, for surgical use**, at Long Beach, D. Dist. Calif.; Civil No. 90-0962RSWL(GHKx). CHARGED 2-26-90: The quality of the article, which was labeled "TTC Products Pure Natural Latex Surgical Gloves Sterile . . . Made In Taiwan," fell below its purported quality since the gloves contained excessive holes—501(c); and the label of the article lacked the name and place of business of the manufacturer, packer or distributor—502(b)(1). DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65828; S. No. 89-425-534 et al.; S.J. No. 11)

Civil Penalty Actions

DEFENDANTS: **X-Ray of Greenville, Inc., and Walter Wilder**, president, Greer, Dist. S.C.; Civil No. 6:84-2665-14. CHARGED 11-1-84, and amended on or about 11-26-84 and 10-17-85 in a suit for injunction and civil penalty: That the defendants were in the business of assembling and installing x-ray systems; that the defendants shipped to and installed at Raleigh and Charlotte, N.C., two x-ray systems and those two x-ray systems did not provide positive beam limitation (PBL); that the defendants failed to bring into compliance, replace, or refund the purchase price of those two x-ray systems—42 U.S.C. 263j(a)(1) and 42 U.S.C. 263j(a)(2); that the defendants had failed to allow FDA to have access to and to inspect records—42 U.S.C. 263j(a)(3); that the defendants failed to provide reports of assembly and/or to issue certifications of compliance with the diagnostic x-ray systems performance standard for nine x-ray systems assembled and installed at varying locations; that the defendants certified compliance with the diagnostic x-ray systems performance standard to purchasers of x-ray systems installed at Chapin, S.C., and Raleigh, N.D.—42 U.S.C. 263j(a)(5)(A); that the defendants failed to file a report of assembly as to the installation of an x-ray unit at Moncks Corner, S.C.—42 U.S.C. 263j(a)(4); that the defendants were well aware of their responsibility to comply with the Public Health Service Act as amended by the Radiation Control for Health and Safety Act of 1968, since the requirement for positive beam limitation had been brought to their attention orally and by

letter on numerous occasions; and that, despite warnings and notices of violations, the defendants had failed to make necessary corrections.

DISPOSITION: The defendants admitted shipping the various x-ray systems but denied that the systems were not in compliance, denied that FDA had not been given access to records, denied failure to issue certification of compliance for x-ray systems installed at the locations except for those systems which the defendants asserted required no certification, and otherwise denied the charges. The government served written interrogatories on the defendants. After the defendants responded to the interrogatories, the government moved for summary judgment. The defendants opposed the government's motions, conceding the underlying facts in most instances, but arguing principals of law and, with respect to three claims, asserting claims whose resolutions depended upon the credibility of witnesses. Accordingly, the government amended its motion for summary judgment in recognition of the need to hear testimony at trial of such three claims.

The court denied the government's motion for summary judgment. The court said that the government's summary judgment matters involved issues of estoppel which the government contended that the defendants might not assert, but that there was no flat rule that estoppel might not run against the government and that the court should hear all the evidence to determine the extent of any penalties to be imposed.

Upon consent of the parties, the case was tried by a U.S. magistrate, who found that the government had proven all of the alleged violations. In the court's final order, the court reviewed the evidence presented at trial. The court stated that the defendants' failure to install PBL (positive beam limitation) at the Raleigh, N.C., installation had "resulted from the defendants' method of reducing costs by selling an old system on paper and replacing it with a new one," which was a clear attempt to circumvent the intention of Congress, and which would be punished by the maximum penalty of \$1,000. The Charlotte, N.C., installation did not appear to have been such a sham transaction, and such violation was to be punished by a penalty of \$500. The defendants' failure to correct the problems at Raleigh and Charlotte, N.C., were to be punished by the maximum of \$1,000 each. The 12 failures to file proper reports of assembly with purchasers were to be punished at \$200 each; and the failure to allow FDA access to certain records was to be punished by a penalty of \$500. Accordingly, the defendants were held jointly and separately liable for the full \$6,900 in civil penalties.

In addition to the civil penalties, the defendants were also enjoined as follows: to either bring the Raleigh and Charlotte, N.C., x-ray systems into compliance with a PBL, or replace the two systems with comparable systems that were in compliance, or refund the costs of the two systems; to permit FDA reasonable access for two years to customer sales invoices and other relevant business records; and to provide FDA and x-ray system purchasers with correct certifications and reports of assembly for those systems which had been installed but not yet certified or reported. (Inj. No. 1076; S. No. 84-482-508 et al.; S.J. No. 12)



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