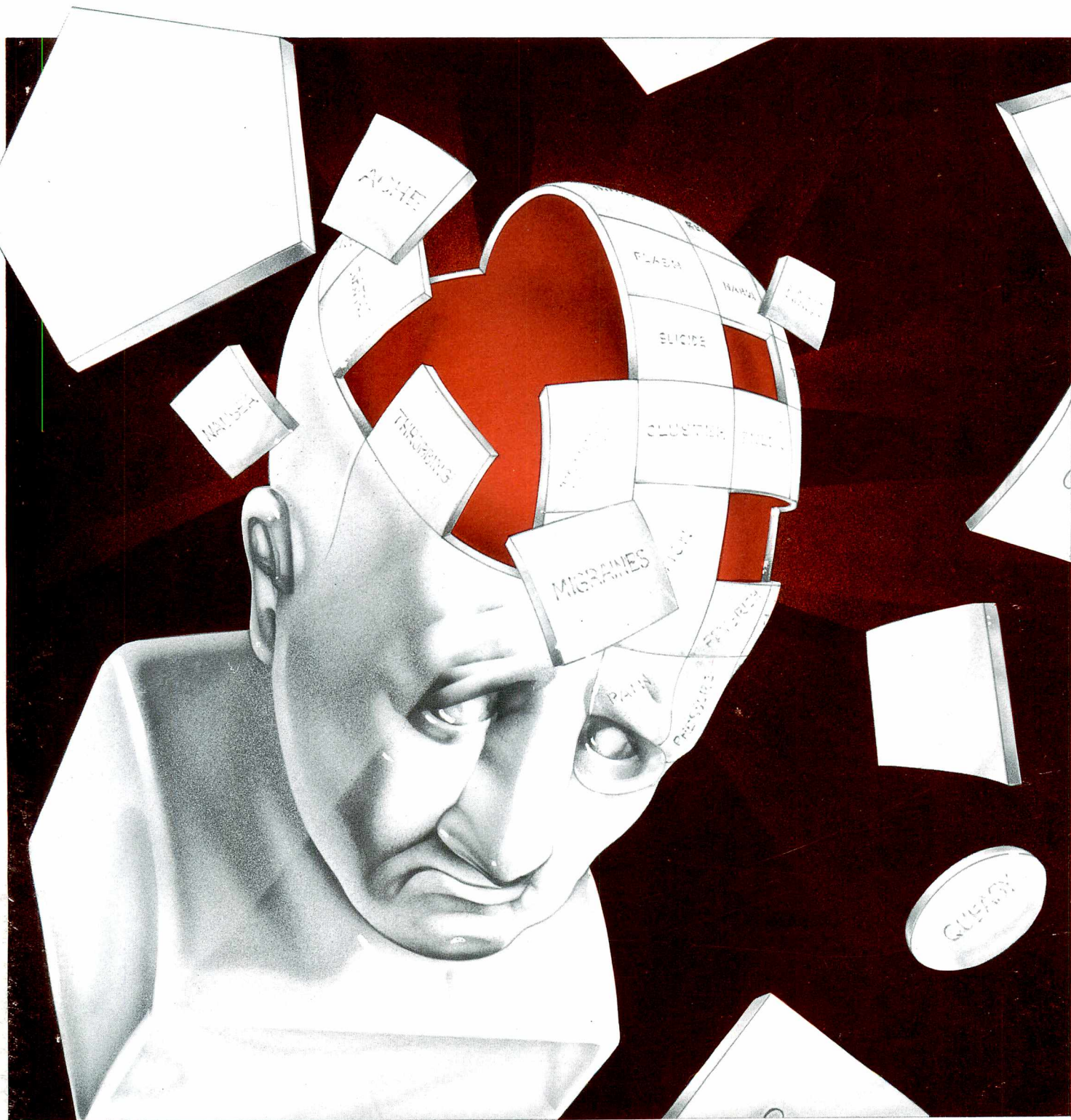


FDA CONSUMER

May 1984

Headaches: Unknown Causes, Uncertain Cures





Deciphering Doctor Talk

Medical language may sound Greek to you, and much of it is based on Greek. However, the way health professionals say things is not all that mysterious and is, in fact, both logical and efficient.

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Irradiation Proposed To Treat Food

Radiation is a possibility for extending the shelf life of and killing bacteria in some foods. It may come to be used on fruits, vegetables, and grains.

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Headaches: Unknown Causes, Uncertain Cures

A common malady, the headache. For some people, all too common. For many, there are remedies. As to causes, that enigmatic virus known as tension gets a lot of the blame.

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The Rise Of Blood Pressure Is Slowed

Here's a success story: More public awareness of hypertension is linked to fewer stroke and heart attack deaths. But 60 million people still have the problem.

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No Menstruation, No Pregnancy = Amenorrhea

Failure to menstruate when there is no pregnancy is a problem for some pre-menopausal women. Exercise and loss of weight may be causes. Sometimes drugs can provide the needed therapy.

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Most M.D.s Keep The Merck Manual Handy (Some Mothers Do, Too)

The 14th edition of The Merck Manual is an instant refresher course for health professionals. Despite its esoteric language, many non-pros also put it to use.

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The Merck Manual—a world of medicine between two covers and a valuable resource for physicians, nurses, and other health professionals. Maybe even for average readers, if they know a bit of medical terminology. See Most M.D.s Keep The Merck Manual Handy, beginning on page 25.

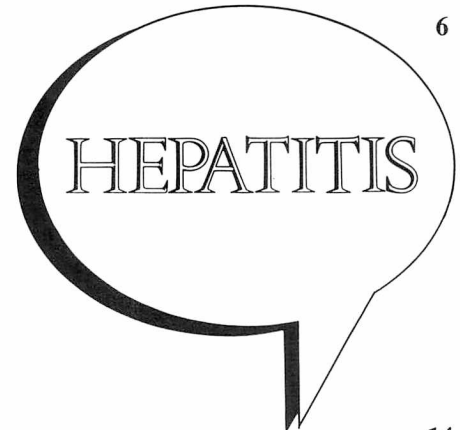
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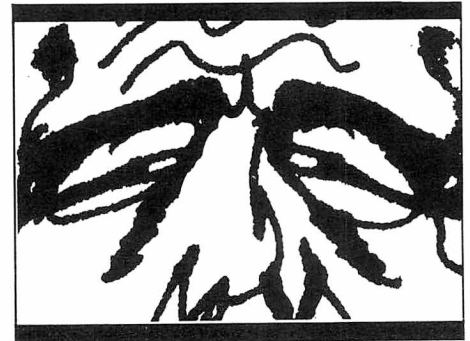
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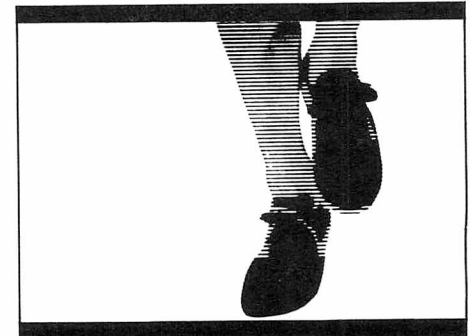
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Drug Controls Preferred

In spite of drug industry claims that FDA regulations are causing a "drug lag," Americans say they want tight regulations and controls on new prescription drugs. A significant 73 percent of the respondents in a Roper poll said they would rather have tight controls and fewer new drugs and thus less risk from products whose side effects are not well known. Only 15 percent would prefer less strict regulation and more new drugs on the market even though this could result in increased risk of injury or death from side effects of the new products. In 1975, 69 percent of people polled wanted fewer drugs and less risk and 19 percent wanted more new drugs.

The public's opinion of the drug industry is higher today than in the previous four years (63 percent had a high or moderately favorable opinion in 1983, compared to 55 percent in 1982). At the same time, 74 percent said that the government must watch industry to be sure consumer products are safe. Well over half the respondents (58 percent) believe that the drug companies are "sitting on" drugs that could help in disease but would not be profitable to them. This opinion was held by 48 percent in 1980.

As in a CBS poll, also reported in this issue's Updates, people polled by the Roper Organization say they do not get enough drug information. A full 61 percent said there is not enough information on the kinds of prescription drugs available for various illnesses; 31 percent said there is.

When it comes to food, diet and health, Americans apparently are getting the message. About 6 in 10 people said they are avoiding or eating very little salt, sugar, desserts and sweets, and sugar substitutes. The percentage of people avoiding salt jumped from 40 percent in 1977 to 63 percent in 1983. (Oddly, avoiding salt was the top means cited by people who said they were trying to lose weight.) Cholesterol and starches are also being watched by more people today than a few years ago. Food firms rated high in the public eye, with

79 percent given favorable ratings, up from 59 percent in 1980.

More people said they control their weight by changing their diets instead of turning to diet books, prescription or OTC drugs, or a psychologist or psychiatrist for help.

Almost all those polled (91 percent) said a well-balanced diet is very or fairly important. Variety in the diet also ranked high in importance. A total of 52 percent said the nutritional value of food is very important, but two-thirds of those polled said it was a good idea to add nutrients to food. Fewer people today think they can get all the vitamins they need from their diets (50 percent in 1983 compared to 58 percent in 1975) and more believe extra vitamins are needed (35 percent in 1983, compared to 25 percent in 1975).

Whether preservatives are added to food was important to 59 percent of the 1983 respondents, compared to 54 percent in 1980 and 61 percent in 1976. Only half considered artificial coloring important, compared to 47 percent in 1980 and 53 percent in 1976.

Roper Organization reports are based on responses from 2,000 adults, representative of the nation as a whole. FDA is one of a number of clients supporting the regular polling.

'Street' Drugs Seized

More than 78 million drug products containing combinations of caffeine, phenylpropanolamine (PPA), and ephedrine were voluntarily destroyed or seized between mid-November 1983 and the end of February 1984. The combinations—bogus recreational drugs—were taken off the market in FDA's program to curb abuse of drug products that were being sold with the implication that they were controlled substances. (See "Drug Combinations Curbed" in Updates, *FDA Consumer*, February 1984.)

As a result of a regulatory letter sent to 377 firms in business in November, these firms destroyed 57,835,547 dosage units. Three seizures,

carried out on FDA's recommendation, netted 20,321,100 dosage units, and seizure of an additional 3,785,950 units was pending. (For more information on such "look-alikes," see "On The Trail Of Counterfeit Drugs" in the December 1981-January 1982 *FDA Consumer*.)

Reprints Available

Reprints are available of the following articles that appeared in the February 1984 issue of *FDA Consumer*: "On Making Food Labels Truthful" and "Hunger Is More Than An Empty Stomach." Single copies of these reprints can be obtained from the Food and Drug Administration, HFE-88, 5600 Fishers Lane, Rockville, Md. 20857. Multiple copies are available from FDA, HFW-40, at the Rockville address. Copies of reprints are also available from FDA's consumer affairs officers, who are located in 30 cities around the country.

Alert On Pacemaker Problem

Cardiologists nationwide have been alerted that certain heart pacemaker leads, manufactured by Medtronic Inc., have an exceptionally high failure rate. Leads are wires that connect the pacemaker with the heart.

The problem lies in the insulation, which may crack and cause an interruption of normal electrical conduction between the pacemaker and the heart. However, the failure can be discovered during routine monitoring, usually performed electronically over telephone lines between the patient's home and the doctor's office. There have been no reports of death or serious injury as a result of a lead failure.

In its letter to 27,000 physicians, Medtronic stated that the failure rate for these leads is about 1 percent during the first year after implant, about 4 percent after two years, and about 10 percent after three years. These failure rates are based on the results of clinical studies conducted at several hospitals in the United States.

The firm recommended the monthly monitoring

of patients with the affected leads. FDA agreed with this advice, adding that physicians should decide whether to implant new leads based on each patient's individual medical condition. Patients should continue to follow the normal instructions recommended by their doctors.

About 26,700 of the leads were manufactured between December 1979 and February 1982. The firm estimates about 18,000 are still implanted in patients. In addition, about 1,200 to 1,500 leads were exported and the firm is notifying purchasers in foreign countries of the problem.

Concern About Rx Drugs

Americans are much concerned about prescription drugs. But even though three-quarters of the consumers recently surveyed by the Columbia Broadcasting System (CBS) feel it's important to have more information about these drugs, only a third consider themselves well informed about prescription drug issues.

In-home interviews in a sample of 1,233 households with a history of prescription drug use during the past five years revealed:

- Nearly half of all prescription-using households borrow prescription drugs from friends or use previously prescribed medication for a similar illness or condition. This is done more often by younger people, less often by those with less education.
- Over one-third of the households use the *Physicians' Desk Reference* for information about prescription drugs; one in five owns a PDR.
- Allergies, infections and blood pressure problems are the most common illnesses in these households, followed by arthritis and stomach disorders.
- Over two-thirds of the households believe it is highly important to have information on blood pressure, heart problems, and life-threatening diseases; about half say it is equally important to have information on all other major illnesses.
- People are only marginally informed about prescription drugs. They say they need more information, particularly about safety and efficacy and

proper home use of prescription drugs.

- Physicians and pharmacists are considered the most useful sources of information about prescription drugs. Friends, family and the mass media are seen as less useful sources.

CBS undertook the study in December 1983 in response to FDA's call for cooperative efforts to do "the kind of research necessary to see what consumers' reactions and perceptions are." The call was made during the moratorium on direct-to-consumer advertising of prescription drugs, requested by the agency earlier that year. Interviews were conducted only in consumer households that had a history of prescription drug use. The results, CBS pollsters said, can be projected to the 77.4 million U.S. households headed by an adult over 24 years of age where prescription drugs have been used during the past five years.

The complete CBS Consumer Model Study Report is available on written request to the CBS Television Network, Marketing Services, 51 West 52 Street, New York, N.Y. 10019, or telephone (212) 975-4163.

No 'Pill'-Cancer Link

Use of "The Pill" is not related to an increased risk of breast cancer, an FDA advisory committee has concluded. The Fertility and Maternal Health Drugs Advisory Committee recently reviewed a number of studies relevant to oral contraceptive use and breast cancer.

One study, conducted by researchers at the University of Southern California School of Medicine, linked an increased risk of breast cancer to the use of "high progestogen" oral contraceptives for an extended period before the age of 25. Dr. Malcom Pike, senior author of the study, which was published in the Oct. 22, 1983, issue of the British medical journal *The Lancet*, presented these views before the committee at a meeting earlier this year.

The advisory committee said that after careful review of the paper by Pike et al. and other studies, it concluded "a significant increase in the risk or development of breast cancer has not been demonstrated for any subgroup of oral contracep-

tive users."

In support of its conclusion, the advisory committee cited a larger study by the U.S. Centers for Disease Control, which presented a re-analysis of its data as well as smaller studies that have shown no significant association between the use of oral contraceptives and breast cancer.

The committee nevertheless recommended that the labeling for oral contraceptives advise women who use them to have annual breast exams along with annual Pap tests for cervical cancer.

The committee also addressed the issue of the progestin content of oral contraceptives—because of the possible adverse effects of progestin on the cardiovascular system. Proposed labeling revisions under review recommend that doctors prescribe oral contraceptives containing the minimum effective quantity of both progestin and estrogen needed by patients.

FDA will review the committee's recommendations before deciding what action to take.

Grant For DNA Product

Alpha-1 Antitrypsin (AAT), a drug of potential value for selected cases of emphysema, is the first recombinant DNA product to be granted FDA orphan drug status since enactment of the Orphan Drug Act of 1983.

AAT is being studied for use in treating some genetically deficient emphysema patients. AAT, a protein produced in the liver of most people, circulates in the blood. One of its functions is to inhibit the activity of elastase, an enzyme that helps destroy bacteria in the lungs. When AAT is lacking, elastase becomes overactive and will attack lung tissue, breaking down the elasticity needed for effective breathing. Of the estimated 54,000 people in the United States who are deficient in AAT, perhaps half may be candidates for treatment.

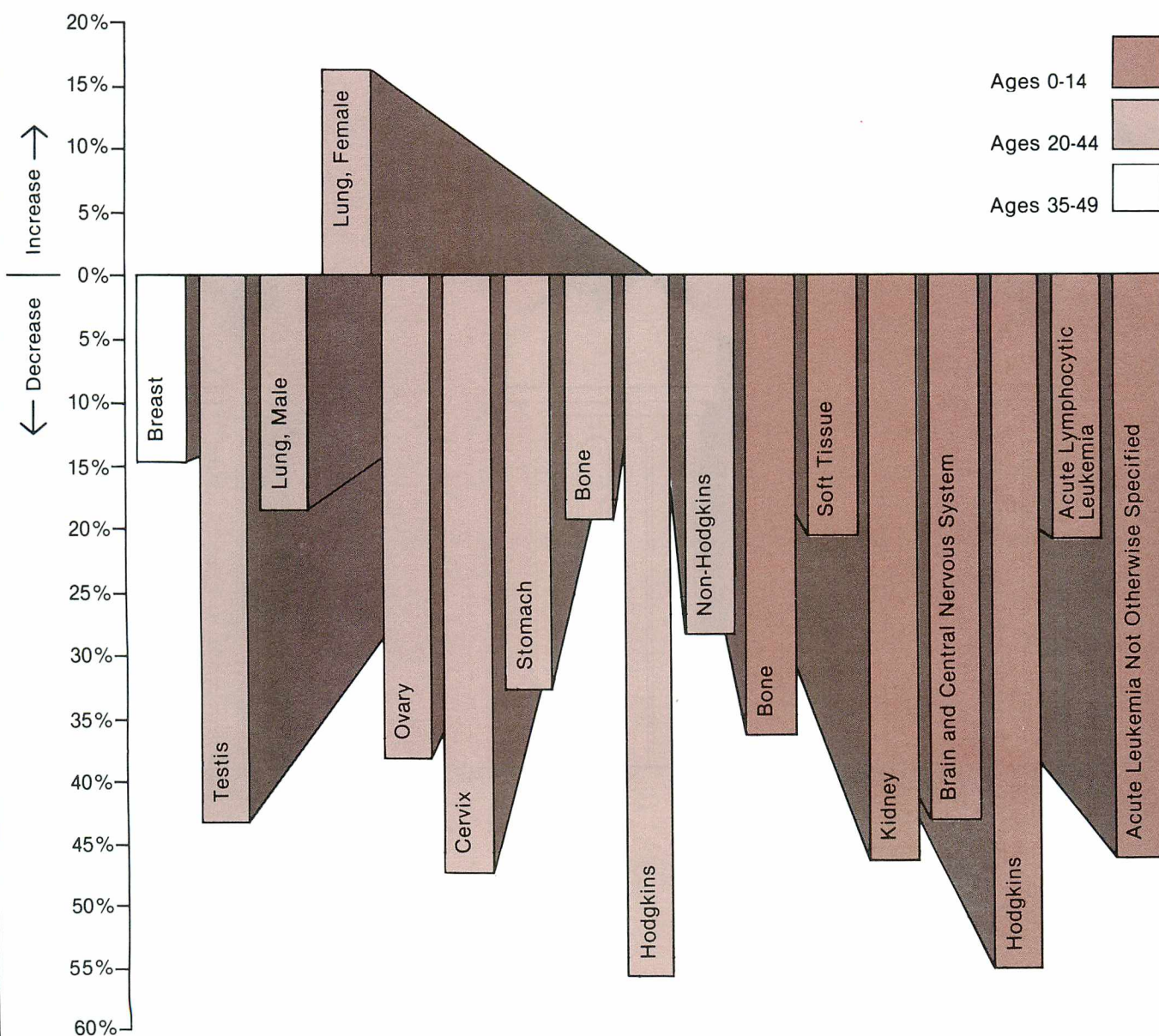
Genetically engineered AAT is produced by inserting a human gene for AAT into another cell for production. The protein also has been isolated from human plasma.

Cooper-Biomedical Inc., Palo Alto, Calif., the company that developed the genetically engineered form of the drug, plans to begin testing the drug soon in patients with deficient blood levels of AAT.

Most Cancer Rates Dropping

Proof that the war on cancer is being won is shown in this graph, depicting the changes in cancer mortality rates between 1968 and 1979. Lung cancer among women is the only category to

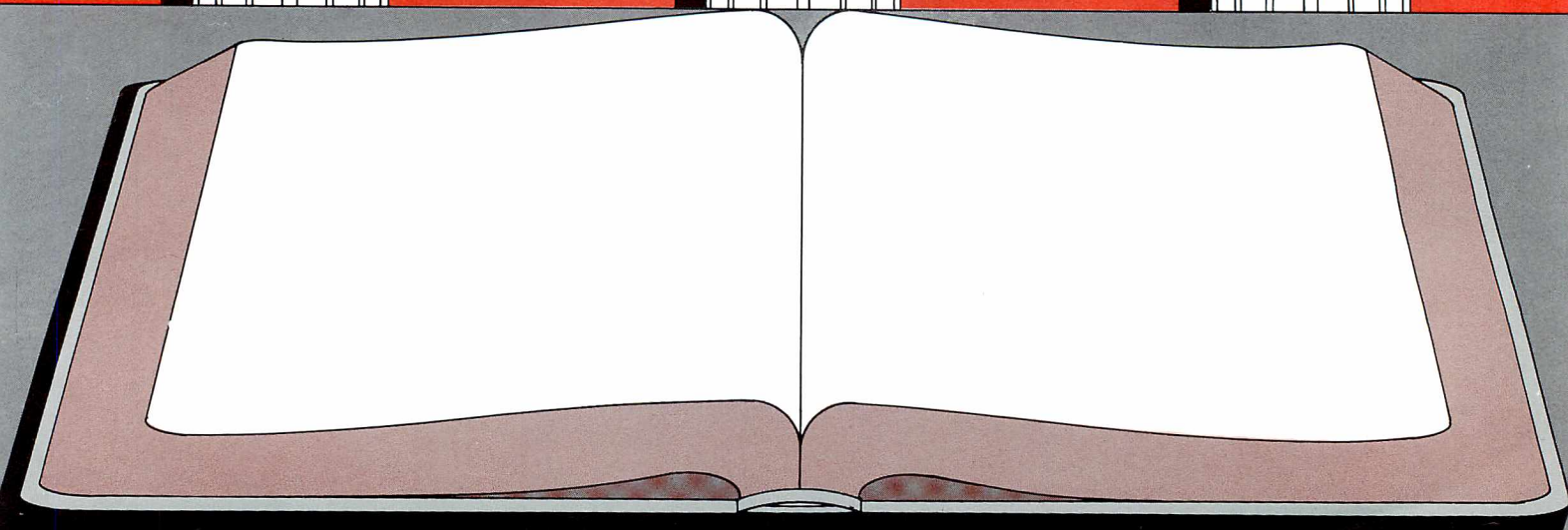
show an increase, probably reflecting the increase in the number of women smoking. The National Cancer Institute has launched a cancer prevention awareness program, stressing care in what one eats, avoidance of cigarettes, and moderation in drinking.



HEPAT

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HEPATITIS



Deciphering Doctor Talk

Hypoglycemia may sound like a difficult word, but its meaning should be apparent to persons with a knowledge of medical terminology. The word parts, all derived from ancient Greek, are *hypo*, meaning under, or deficient; *glyco*, referring to sugar; and *emia*, referring to blood. When put together, the word hypoglycemia means an abnormally low level of sugar in the blood.

Thousands of medical words can be constructed in the same manner. To the famed Greek physician Hippocrates, who lived from 460 to 377 B.C., goes the credit for contributing to modern medical language most of these mix-and-match prefixes, suffixes and root words.

The Romans adopted Greek medicine and most of the terminology used by Greek physicians by the third century B.C., although they often gave the words Latin spelling. The use of Latin and Greek in medical terminology received new currency during the Renaissance when these languages became the medium of intellectual inquiry, providing a ready source of medical words for physicians of the times. Translations of Arabic medical texts also contributed new terms.

Modern medical terminology thus consists largely of Greek words and roots that have been Latinized. (Only a few purely Latin words have survived, and these are associated primarily with anatomy.) According to *Dorland's Illustrated Medical Dictionary*, 75 percent of the scientific words commonly used can be traced

to these ancient languages. Other words are of more modern origin and come to us from French or German.

Some medical terms are based on a single root. For instance, "muscle" comes from the Latin "musculus"—a little mouse—describing the way certain muscles move under the skin. Coccyx, a small bone at the base of the spine, gets its name from the fact that it looks like the bill of the cuckoo, or *kokkyx*, in Greek.

Most medical words combine two or more words or word elements to form a new word. Because ancient Greek and Latin are "dead" languages, the meanings of these elements have not changed over the centuries. Thus, medical terms formed from them are logical and precise. The combinations have become a kind of condensed language that doctors the world over can understand.

Although it is true that doctors of old wrote their prescriptions in Latin to keep the patient from knowing what was in them, modern medical personnel don't use medical terminology to confuse the patient. It's just more convenient to use these universally accepted terms. For example, it's easier to say "arthritis" than "inflammation of the joints."

Here's a sampling of the bits and pieces that make up some familiar medical language.

Prefixes

a, an = without, not
ad = near
anti = against

(continued)



HEMO RRHAGE

Prefixes (Continued)

end(o) = within
ep(i) = on, upon, over
hyper = above, over, excessive
hypo = below, under, deficient
inter = between
intra = within
macro = large
micro = small
peri = around
pre = before, in front of
poly = many

Combining Forms*

angio, angi = blood or lymph vessel
arterio = artery
arthro = joint
brady = slow
cardio = heart
chole, cholo = bile
colo = colon
cysto, cystido = sac, cyst, bladder
dys = difficult, painful, abnormal
glyco = sugar
hema, hemo, hemato = blood
hepato = liver
hystero = uterus
leuco, leuko = white
lipo = fat
meno = menses
nephro = kidney
osteo = bone
pneumato, pneuma = air, gas
rhino = nose
sclero = hard
tachy = swift, rapid
veno = vein

*Combining form = root
word + a vowel

Suffixes

algia = pain
cyte = cell
ectomy = excision of
emia = blood
itis = inflammation of
megaly = very large
oma = tumor, swelling
osis = disease, morbid process
ostomy = artificial opening
otomy, tomy = incision into
pathy = disease of
pnea = breathing
rhage, rhagia = bleeding, bursting
forth
rhea = flow
uria = urine

By combining root words with
prefixes and suffixes, words such as the
following are formed:

arteriosclerosis = hardening of the
arteries
bradycardia = slowness of the
heartbeat
colostomy = surgical creation of
an opening between the colon and
the surface of the body
dyspnea = difficult or painful
breathing
glycosuria = presence of sugar in the
urine
hemorrhage = escape of blood from
the vessels; bleeding
hepatitis = inflammation of the liver
hepatomegaly = enlargement of the
liver
hyperlipemia = excessive fat in the
blood
hysterectomy = removal of the uterus

DYS PNEA



intravenous = within a vein or veins
 leucocyte = white blood cell
 lipoma = a fatty tumor
 macrocyst = a large cyst
 neuralgia = severe sharp pain along
 the course of a nerve
 periangioma = a tumor which sur-
 rounds a blood vessel
 rhinitis = inflammation of the nasal
 passages

For a blockbuster of a medical word
 there is "hepatocholangiocystoduoden-
 ostomy," which any student who has
 done the required homework knows
 means "the establishment of drainage
 of bile ducts into the duodenum
 through the gallbladder."

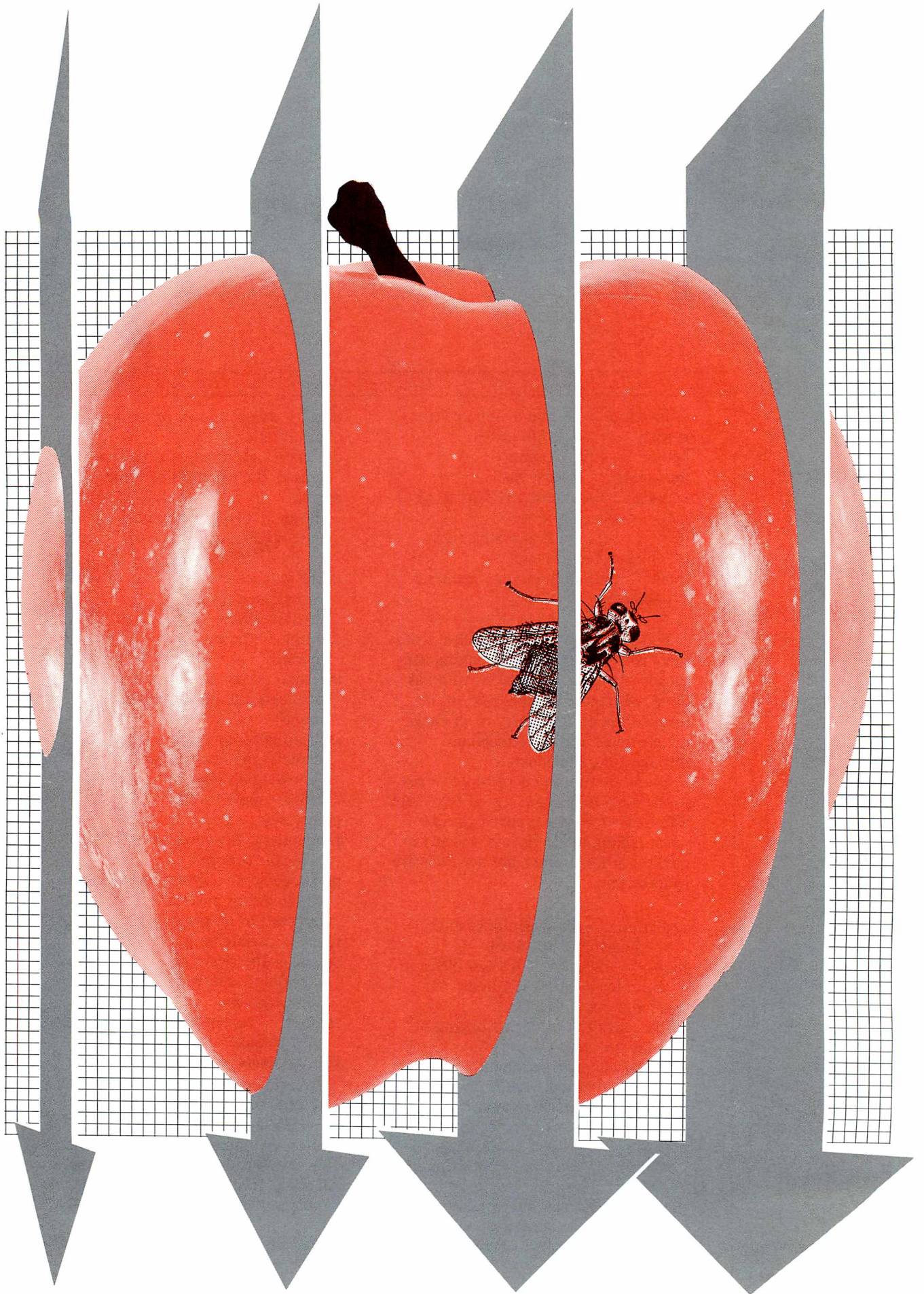
There are thousands of other words
 in the medical lexicon. Listed below are
 a few that a patient might well hear
 when talking to the doctor, or read in
 medical articles. Some are not exclusive
 to medicine:

arrhythmia = an irregularity in the
 rhythm of the heartbeat
 biopsy = removal of a small piece of
 tissue for examination under the
 microscope
 cardiac arrest = sudden stopping of
 heart function
 cardiovascular = pertaining to the
 heart and blood vessels
 caries = gradual decay and
 disintegration of bone or tooth
 comatose = in or of a coma, an
 abnormal deep stupor occurring in
 illness
 contraindication = any condition
 that renders some line of
 treatment improper or undesirable

data = things known or assumed;
 information
 diuretic = an agent or drug that in-
 creases the secretion of urine
 edema = local or generalized con-
 dition in which the body
 tissues contain an excessive amount
 of fluid; swelling
 efficacy = power to produce effects
 or intended results;
 effectiveness
 etiology = the cause(s) or origin of a
 disease
 ingestion = the act of taking food,
 medicine, etc. into the body by
 mouth
 myocardial infarction = death of
 tissue in the heart muscle, usually
 following an interruption of the
 blood supply to the heart
 pathogenic = productive of disease
 prognosis = the forecast as to the
 probable outcome of a disease
 psychogenic = a symptom having an
 emotional or psychologic origin, as
 opposed to an organic one
 renal = pertaining to the kidney
 serum = the clear portion of any ani-
 mal fluid, separated from its more
 solid elements
 stenosis = constriction or narrowing
 of a passage or opening
 subcutaneous = beneath the skin

Consumers who turn to sources such
 as *The Merck Manual* or the *Physi-
 cians' Desk Reference* for health infor-
 mation may need a medical dictionary
 close by. But once the Greek and Latin
 roots are mastered, they should be able
 to solo without lexicographic assistance.

—Evelyn Zamula and Annabel Hecht



Irradiation Proposed To Treat Food

by Chris Lecos

In the not-too-distant future, American shoppers can expect to buy foods treated with radiation to control insect and bacterial contamination. Although this may make some consumers uneasy, the Food and Drug Administration says the foods will be safe and wholesome to eat.

More than 30 years of research, most of it government sponsored, has gone into food irradiation. After years of careful study and review of this research and technological development, FDA has proposed a regulation that would expand uses of ionizing radiation on such foods as fresh fruits, vegetables and spices. In the early 1960s, FDA issued regulations allowing processors to irradiate wheat and wheat flour to control insect contamination and to irradiate potatoes to slow the development of sprouts. However, no commercial uses ever resulted.

In announcing its latest proposal, FDA stressed that this treatment of food at the levels of radiation proposed would add no radioactivity to the foods, nor would it expose consumers to any radioactivity. "Food that is not made radioactive cannot expose consumers to radiation," the agency emphasized, adding that the type of radiation to be allowed "will not induce in foods any radioactivity that can be detected, even by methods that detect the presence of radioactive isotopes that occur naturally in all foods."

Although irradiation does not make food radioactive, it can produce chemical changes in it. A special committee formed by FDA's Bureau of Foods reviewed the world's scientific literature on the effects of irradiation and concluded that any changes that would occur in food are inconsequential compared to changes that occur normally in storage or in cooking. FDA scientists also note that in all studies in which irradiated foods were fed to animals over many generations, no adverse effects were found that could be attributed to the irradiation, a point also made by international and regulatory groups in other countries.

Currently, many foods are treated with chemical additives, pesticides, or some other substance to protect them from insect and microbial contaminants and to give

them extended shelf life. Irradiation presents another prospect for maintaining the quality of foods. It might be used, for example, as a replacement for the controversial fumigant ethylene dibromide (EDB), to control insects in certain agricultural products. EDB is a known animal carcinogen (cancer-causing agent).

As announced in the *Federal Register* on Feb. 14, FDA is proposing:

- To permit such foods as fresh fruits and vegetables to be treated with a dose level not to exceed 1 kilogray (the equivalent of 100 kilorads or 100,000 rads of radiation to inhibit the "growth and maturation" of the products as well as to kill insects that are present after harvest. In other words, the proposal would allow irradiation to keep fruits and vegetables from spoiling, thus extending the shelf life for both sellers and buyers. That level of irradiation also would permit growers to treat products for the kind of insect infestation that occurred several years ago in California and Florida, where citrus and other crops were threatened by the Mediterranean fruit fly (Medfly).
- To allow the treatment of a wide variety of spices, including dried and dehydrated onions and garlic, with a

Irradiation doses are measured in rads. The term "rad" is shorthand for "radiation absorbed dose." A low dose for food irradiation is in the range of 0 to 100 kilorads; a medium dose is 100 to 1,000 kilorads or 1 megarad; a high dose is 1,000 to 5,000 kilorads or 1 to 5 megarads. A kilorad is equal to 1,000 rads; a megarad is equal to 1 million rads. In more recent years the term "gray" (Gy) also has been used to describe dose levels. One hundred rads equals 1 gray.

dose level of up to 30 kilograys to kill insects or bacteria in the products. FDA officials pointed out that the higher dose level could be allowed because spices are used in small amounts that make no nutritional contribution to the human diet. However, like some other food ingredients, spices may contain high bacterial loads, and, when the bacteria-laden spices are added to processed foods, they can be sources of contamination.

Technically, the regulation would allow the use of irradiation—up to the 100-kilorad maximum—on any food where insects may be a problem. As a practical matter, however, its main uses would be with foods such as fruits, vegetables, spices and grains.

A key part of FDA's proposal states that food treated with ionizing radiation "shall receive the minimal radiation dose reasonably required to accomplish its intended technical effect and not more than the maximum dose specified by the applicable regulation." Thus, despite the 100-kilorad ceiling, FDA would expect industry to use only as much radiation as would be needed.

The maximum dose is not needed, for example, to prevent potato sprouting. The 100 kilorads "would turn the potatoes into mush," an FDA scientist explained. Only 5 to 15 kilorads are needed to keep potatoes from sprouting. That is the limit FDA permits in its existing regulation for this use.

Companies that plan to irradiate food would be expected to specify the procedure they would use and the dose levels. In addition, industry must be able to demonstrate to FDA upon request that its irradiation procedures were established by experts qualified in radiation processing.

Under the proposal, FDA also would monitor industry compliance with requirements. Food producers would be required to maintain records of radiation doses used for up to one year past the expected shelf life of a product, with all records subject to examination by FDA inspectors.

Besides complying with FDA's irradiation regulation, food processors would have to adhere to federal plant and worker safety requirements of the Nuclear Regulatory Commission and the Occupational Safety and Health Administration.

Irradiated foods shipped in bulk to a processor for further processing must bear a labeling statement that says: "Treated with ionizing radiation—do not irradiate again." The wording would have to appear on the container and on any invoices or bills of lading.

Foods sold at retail would not be labeled to indicate that they had been treated with irradiation. However, FDA invited public comment on retail labeling, and the proposal will not become effective until after the agency has reviewed all comments and has published a final regulation.

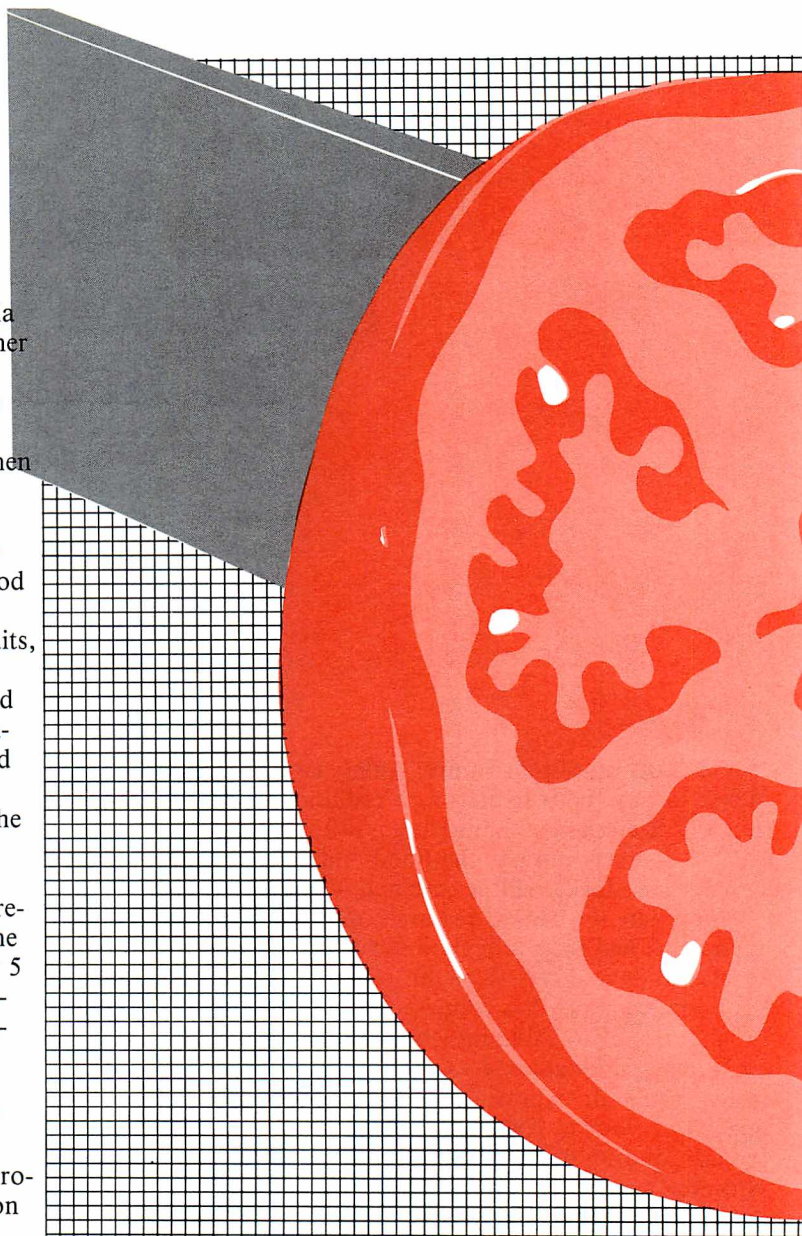
FDA's responsibility for regulating the irradiation of foods comes under the 1958 Food Additives Amendment

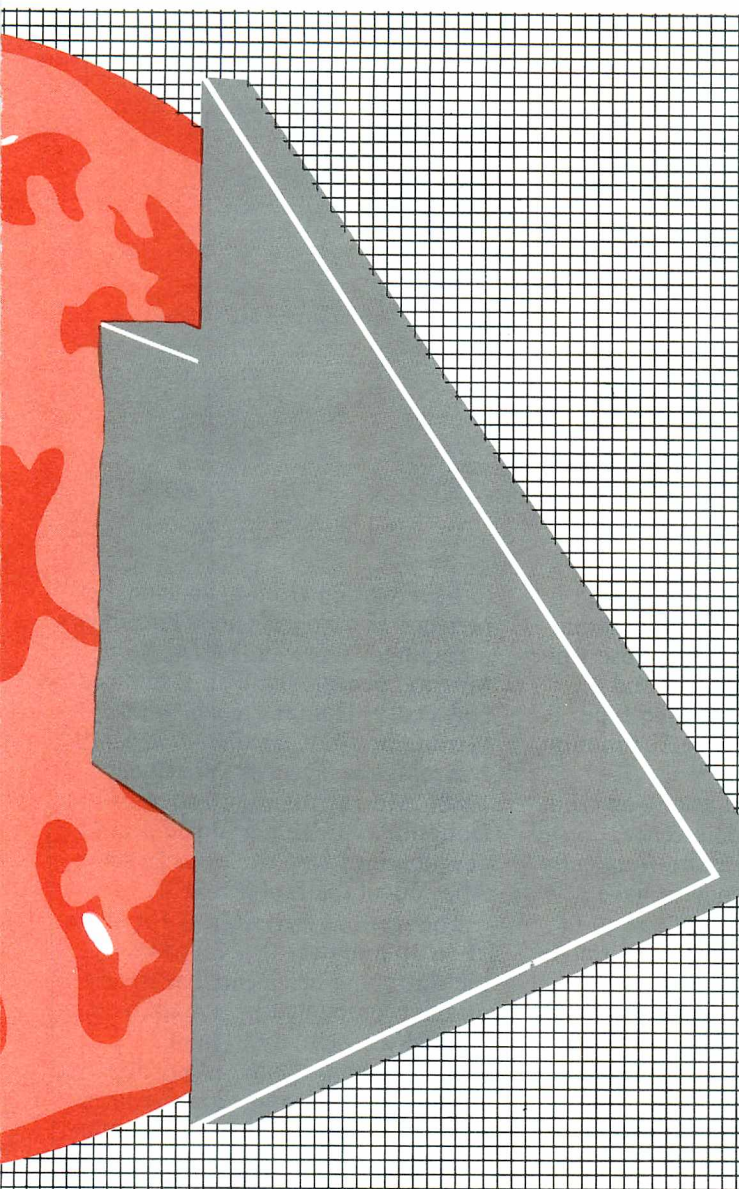
to the Food, Drug, and Cosmetic Act, which classified irradiation as a food additive. Thus, if a food firm wants to use irradiation, it must demonstrate the safety of its process to FDA's satisfaction before the treated food products can be marketed.

The irradiation of foods has worldwide implications. It is viewed by economic experts as a means of increasing food supplies. It could also mean expanding exports of American agricultural products. The process could help save some of the estimated 25 to 30 percent of the world's food supply that is lost each year because of pests and spoilage.

A number of countries already allow certain foods to be irradiated. The Food and Agriculture Organization of the United Nations, International Atomic Energy Agency, and World Health Organization have issued general standards for irradiated foods. The Institute of Food Technologists reported recently that between 1958 and 1981, 24 countries had approved irradiation treatment of some 40 foods.

A report issued last November by the U.S. Department of Commerce's Bureau of Industrial Economics predicted that "many important domestic and international markets





for irradiated foods could develop if FDA permits the use of irradiation technology.” The U.S. Department of Energy also has been interested in food irradiation, spending about \$7 million annually on its development. One of the byproducts of spent nuclear fuel processing is cesium-137, a potential source of radiation for food. The Commerce Department report noted: “Any use of cesium-137 for irradiation substantially reduces the disposal cost of nuclear plant wastes.”

There is nothing new or revolutionary about the idea of using radiation on foods. As far back as 1908, a technique was developed by a Philadelphia man for killing tobacco pests with X-rays. Twelve years later, a French scientist discovered that ionizing radiation could be used to preserve food.

The World War II need to feed millions of men and women in uniform brought renewed interest in food irradiation. In 1943, the U.S. Army asked the Massachusetts Institute of Technology (MIT) for its view of whether the shelf life of food could be extended by irradiation. By 1947, MIT reported that the process was feasible. In 1953, various federally funded irradiation

research projects were under the Army Quartermaster Corp’s Research and Development Command Laboratory in Natick, Mass. There, fruits, vegetables, dairy products, fish and meat were exposed systematically to gamma rays and other forms of energy bombardment.

Most of this early research was federally sponsored, and enough attention had been focused on the issue to prompt Congress, when it passed the 1958 food additives legislation, to adopt specific provisions on food irradiation. The legislation permits FDA to adopt new regulations permitting food irradiation uses, and it empowers FDA to take action if a food has been intentionally irradiated without a regulation covering the proposed irradiation use. “Obviously,” the preamble to the proposed regulation notes, “Congress did not intend that the radiation itself be tested, but rather its effects on food.” Thus, FDA continued, “to issue a food additive regulation for the source of radiation, the agency must be assured with reasonable certainty that no harm will result from the proposed use.”

It is difficult to predict how wide the future uses of food irradiation will spread. Much depends on industry interest and willingness to make the substantial investment the technology demands.

When food is irradiated, most of the radiation energy passes through the food without being absorbed. However, some of the rays do not pass through the food. This absorbed energy slows maturation and kills insects.

Irradiation is sometimes described as a “cold” process because it does not cause a significant rise in the temperature of food. The irradiation—through gamma rays, electron beams, or by X-rays—does cause chemical changes in a food, producing new chemical substances called radiolytic products. The extent of change and the amount of radiolytic products that result depend on the amount of radiation absorbed. Because each food varies in its chemical composition, the changes from irradiation differ among foods.

Even small changes that may pose no safety concerns can affect flavor, texture and other characteristics. These might be unnoticed by some consumers but discernible to others. But these changes are not produced by irradiation alone. Most processing techniques—including cooking, canning and freezing—have some effect on the flavor and texture of foods.

Over the years, there has been considerable research on the various radiation doses of foods so that, in effect, scientists have a pretty good idea what range of radiation is generally needed for specific effects. Meanwhile, the agency has issued this cautionary statement: “The exact dose that will achieve a particular effect in a specific food without otherwise damaging the food is not yet known in all cases . . .” Further research is needed before acceptable dosage levels can be determined for commercial uses.

Chris Lecos is a member of FDA’s publications staff.



Unknown Causes, Uncertain Cures

by Annabel Hecht

Headache is a common and universal complaint. Every language has a word for it. In German, it's *Kopfschmerz*; in French, *mal de tête*; and in Spanish it's called *dolor de cabeza*. No matter what the language, it comes out the same—a pain in the head.

Headaches come in all degrees of severity. Some are just a passing annoyance; others cause such suffering as to drive the victim to thoughts of suicide. A headache may be a steady, persistent pain or it may be a throbbing sensation. Some come on suddenly, like a lightning bolt; others develop gradually. The pain may be concentrated on just one side of the head, may center around the eyes and sinus areas, or encompass the entire area from the eyebrows to the nape of the neck.

Painful as it may be, a headache is not a disease. It may be a symptom of some underlying condition, such as a sinus infection. However, the vast majority of headaches are not explained by underlying disease or pathology. Indeed, most headaches in adults, even prolonged ones, are related to tension.

Few headaches are as devastating as the migraines and cluster headaches. These are classified as "vascular headaches of the migraine type" because they are thought to be associated with changes in the blood vessels in the head. It is estimated that 10 to 20 percent of the U.S. population suffers from recurrent migraine and cluster headaches. For a good many of these people the pain, nausea and other symptoms are disabling.

There are two types of migraine, the classic type that occurs in about 10 percent of migraineurs (those who suffer from this condition) and a more frequently encountered type, called (as one might expect) common migraine.

Migraine can begin at any age, but it usually starts in adolescence. Women are afflicted more frequently than men. The tendency to have migraine headaches seems to run in families. Sufferers often recall watching their mother or other female relative retire to a darkened room with a "sick" headache.

Basically, a migraine headache can be described as a throbbing, recurrent headache, usually felt on one side of the forehead or around one eye. It may start on one side of the upper neck, forehead or temple and move to the other half or the entire head. Victims of the classic migraine usually have a warning of an impending attack. This forewarning, known as an aura or prodrome, is characterized by visual distortions called scotoma. A blind spot may appear in the visual field. Or the patient may see glittering and scintillating forms, often with zigzag borders. Such shapes are called fortification spectra because they look like a bird's-eye view of a fortified town.

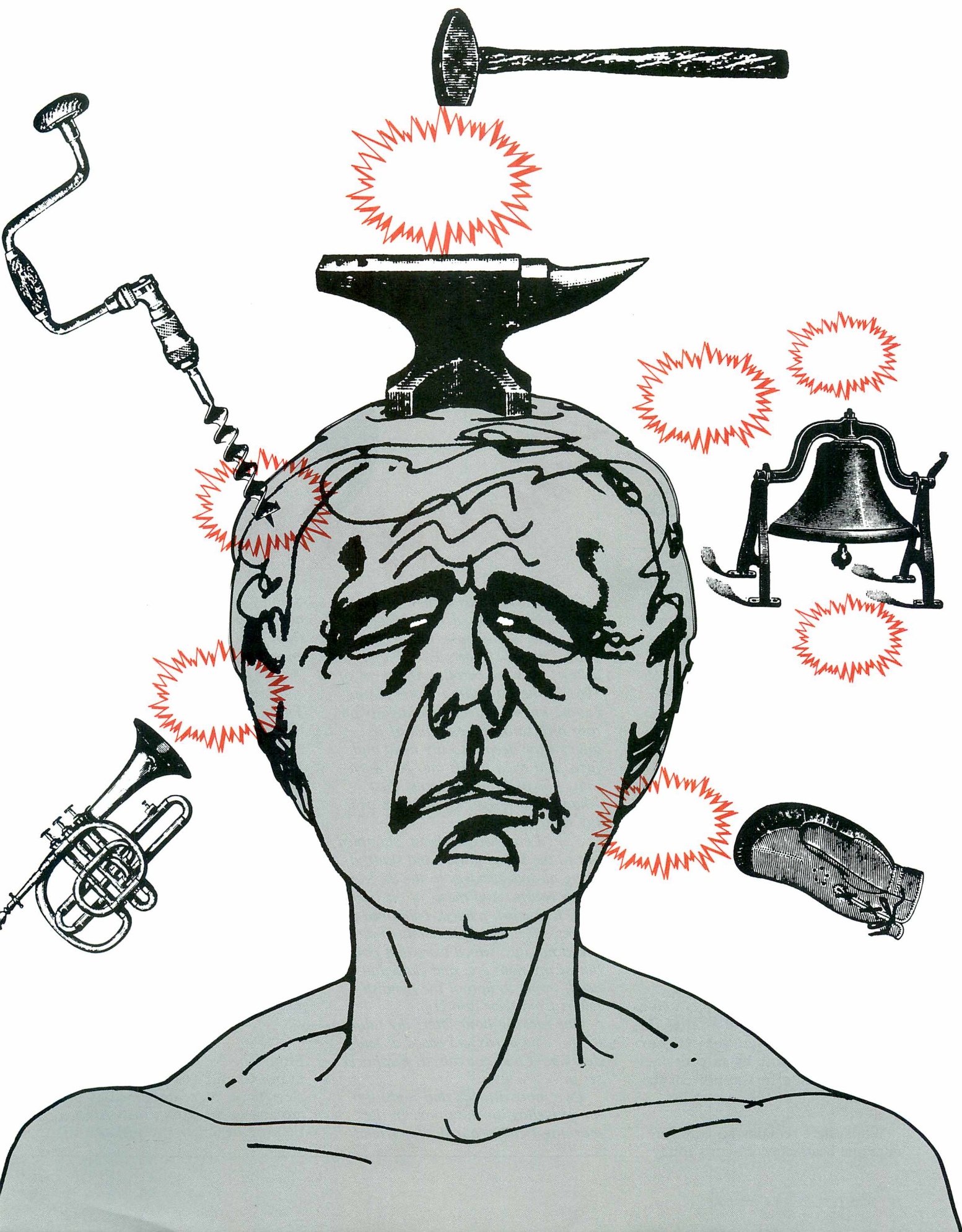
Strange hearing and taste sensations also are a part of this warning phase. These bizarre sensations have been dubbed the "Alice in Wonderland syndrome" because of the similarity to the distortions in size, position and place experienced by Alice in her adventures. Author Lewis Carroll (in real life, Charles Dodgson) is said

to have written from his personal experience as a migraineur. (This theory is disputed, however, by Dr. T.J. Murray, neurologist with Dalhousie University, Halifax, Nova Scotia. Writing in *The Canadian Journal of Neurological Sciences* [November 1982], Murray maintains that Dodgson's initial migraine did not develop until 28 years after he sent Alice down the rabbit hole.)

The warning period lasts for about 15 to 30 minutes. It is followed by the throbbing headache that is very often accompanied by nausea, vomiting and a sensitivity to light (photophobia). Chills, fever, dizziness, diarrhea, and excessive urination as well as arm, leg or abdominal pain frequently occur. The headache usually reaches its greatest intensity in about an hour, and many go on for several hours.

In common migraine the aura is less sharply defined and may occur several hours or days before the actual headache begins. The two types of migraine share many symptoms, including irritability, pallor, dizziness and sweating. Migraine can waken its victims during sleep. Common migraine attacks last from several hours to several days.

The pain of migraine is the result of a series of changes in the blood vessels of the scalp as well as those supplying the brain. First, these vessels constrict, producing the sensory disturbances that mark the warning stage of the migraine. The same blood vessels then dilate, releasing chemicals that result in the throbbing headache. A number of these chemicals
(continued)



calcs are associated with inflammation; and it is believed that a local inflammatory reaction, along with swelling of the tissues around the blood vessels, plays a part in the painful stage of migraine.

What triggers these changes in the blood vessels is not entirely clear. A wide variety of factors have been suggested, including changes in sleep patterns, irregular eating habits, temperature extremes, sudden changes in barometric pressure, cigarette smoke, perfume, and glaring lights.

Some people believe certain foods, such as aged cheese, some wines and chocolate, may trigger migraine attacks, although the role of diet is still controversial.

Hormones may also be involved. Many women have migraine attacks preceding their menstrual periods. One of the adverse reactions associated with oral contraceptives is migraine, a fact noted in the information provided to women on the pill. Estrogens taken to relieve symptoms of menopause also may trigger migraine headaches.

Migraineurs are sometimes stereotyped as rigid and compulsively perfectionistic, proud of their accomplishments, and demanding in personal standards of behavior. Such personality traits do not fit all migraine victims, and many people who are rigid and demanding do not suffer from these headaches. However, some migraine specialists believe that when perfectionists are under stress they are more likely to have headaches.

Over the years, medical efforts to bring migraines to a halt have included vitamin therapy, inhalation of 100 percent oxygen, and even surgery. Tonsils, appendices and thyroid glands have been removed, as well as portions of the temporal arteries. In the 1930s, women were subjected to artificial menopause by surgery or radiation in an effort to prevent the headaches. All of this was to no avail.

While there remains no cure for migraine headaches, doctors today

'The Angry Claw' of Pain



Outwardly, I was a calm producer-director; inwardly, a vat of seething sour wine. Some bung had to blow. It blew. On New Year's Eve. Paper hats askew, we were caroling the birth of 1961 in the La Quinta Hotel dining room, when suddenly—a huge phantom bird sank three talons of its angry claw deep into my head and face, and tried to lift me. No warnings, nor preliminary signs. Just wham! A massive, killing pain over my right eye.

. . . I clutched my head, stumbled out to the broad lawns, and skulked along oleander hedges to the deserted tennis courts. And there, in the darkness, I moaned, panted, ballooned my cheeks, blew out short bursts of air, licked hot lips, wiped tears that poured out of my right eye, and clawed at my head, trying to uproot the fiendish talons from their iron grip.

One racking hour later, the talons let go. The paroxysm eased as suddenly as it had convulsed. Euphoria set in . . .

Two more attacks that night left me groveling on the floor. In the morning I called our doctor friend

Stanley Imerman. Three different neurologists examined me; tumping, thumping; X rays of the head, encephalograms of the brain waves. All normal. The agonizing attacks continued nightly—two, three, four. There is no known cure for "cluster" headaches, said the experts . . .

No one on the set, not even Art Black, my assistant, or Frank Capra, Jr., my second assistant, knew of the nightly ordeal. But my son did notice that instead of whistling in the morning, I came in with a face that looked like something a cartoonist had etched in over-ripe liver, and that in between set-ups I would also break down and beseech the Almighty with a "gimme" prayer: "Lord, I can take the damn headaches at night and still shoot this film. But please, don't let me get them in the daytime . . . not in the daytime, please . . ."

From *The Name Above The Title* by Frank Capra, The MacMillan Co., New York, N.Y. Reprinted by permission of William Morris Agency, Inc., on behalf of the author.

may use a variety of approaches to treat victims. These approaches include changes in diet and lifestyle as well as a number of drugs. Common analgesics, such as aspirin, acetaminophen and propoxyphene, or small doses of codeine may ease a mild attack, if given early enough. Ergot alkaloids may be prescribed for acute attacks. Taken at the first sign of an aura, these drugs work by constricting the blood vessels, thereby preventing the dilation phase of the migraine cycle. They do not have any painkilling or sedative effects, however.

Ergot is available as a single ingredient in an injectable form, as an inhalant, or in solid forms that can be given orally, sublingually (to be dissolved under the tongue), and rectally as a suppository. It is also marketed in combination with other drugs such as caffeine, belladonna alkaloids, and pentobarbital. These drugs help constrict the blood vessels, control nausea, and relax the patient. Brand names of ergot preparations include Cafergot, Cafergot P-B, D.H.E. 45, Ergostat, Gynergen, Medihaler Ergotamine, and Wigraine.

Drug dosage should be tailored for each patient. Ergot preparations should not be given to patients with peripheral vascular disease, coronary heart disease, hypertension, or impaired kidney or liver function. The side effects include numbness and tingling of fingers and toes, muscle stiffness, gastric irritation, nausea and vomiting, lightheadedness and drowsiness. Ergot poisoning also is a possible, though rare, adverse reaction.

Another drug that is used to relieve migraine headaches is isometheptene mucate. In a single ingredient product (Migralam) or in combination with dichloralphenazone and acetaminophen (Midrin), this drug acts by constricting the dilated blood vessels in the head. It should not be given to patients who have glaucoma, severe kidney disease, liver disease, organic heart disease, hypertension, or who are taking a class of drugs called

MAO inhibitors. Adverse reactions are transient dizziness and skin rash.

For migraineurs who have one or more attacks a week or whose headaches are uncontrollable or so severe they must be prevented regardless of how often they occur, there are drugs that sometimes may block the onset of migraine attacks. Methysergide maleate (Sansert), a relative of LSD, prevents or suppresses migraine by inhibiting serotonin, a chemical involved in the mechanism of vascular headache. The drug is of no use once the attack has started.

Adverse reactions that occur in many patients include stomach discomfort, muscle cramps, edema, numbness, tingling of limbs, and depression. Long-term use can lead to a serious condition called retroperitoneal fibrosis. This is a growth of fibrous matter behind the peritoneum, the membrane lining the abdomen. Symptoms of this condition include chest pains, flank or groin pain, leg cramps, shortness of breath, and swelling of hands and ankles. Because of these side effects, the drug should not be used for more than six months at a time and a drug-free interval of three to four weeks should be observed between each course of treatment.

Propranolol (Inderal) is usually thought of as a treatment for high blood pressure and angina, but it can also be used to prevent common migraine headaches. One of a class of drugs called beta adrenergic blockers (see "Drugs That Block For Ailing Hearts," November 1983 *FDA Consumer*), propranolol acts in migraines by blocking receptors in the walls of arteries, thus preventing their dilation. It is not effective once the headache has started.

Propranolol is not without its side effects, including precipitation or worsening of heart failure and asthma. If the drug doesn't seem to be effective after four to six weeks, it should be discontinued.

Although cluster headaches and migraines are both classified as

vascular headaches, they differ in a number of ways. There are no scintillating visual distortions to warn that a cluster headache is about to begin, nausea and vomiting are rare. Victims of cluster headaches are usually men in the 20 to 40 age bracket.

Cluster headaches are aptly named, for they come in clusters, striking several times a day for a week or more, sometimes for months. (They also are called migraine variants or histamine cephalgia.) After a bout, the headaches may not occur again for long periods, during which the patient is without headache symptoms.

The pain of cluster headaches comes on suddenly, often in the middle of the night, and lasts 10 minutes to several hours. It can only be described as excruciating. There is a tightness in the head as if it is in a vise. One victim describes sensations such as a hot poker boring and burning under the scalp. During an attack the victim may clutch at his head, dig at his eyes, or go through other violent motions. "You want to tear your head off and throw it out the window," a sufferer says.

Cluster headaches occur on one side of the head only, although the pain may change sides during different clusters. The eye on the painful side becomes red and teary and the eyelid is swollen. The nose on that side becomes stuffy and runny. The patient's head may be sensitive for a time after the headache is relieved.

Again, medical science doesn't know what causes cluster headaches. Some medical texts suggest a triggering factor may be alcohol.

Treatment of cluster headaches is very similar to that of migraine. The ergot preparations and methysergide maleate are the drugs of choice, but they must be used early in the attack to be really effective.

Like migraine, there is no cure for cluster headaches.

Annabel Hecht is a member of FDA's publications staff.

The Rise Of Blood Pressure Is Slowed

by Larry Blaser

There's good news and bad news about high blood pressure.

The good news is that more and more people are controlling the problem.

The bad news is that high blood pressure continues to be a problem to some degree for more than 60 million Americans.

The fact that more people are keeping their hypertension under control has contributed substantially to a dramatic reduction in deaths from stroke and coronary heart disease. In the decade from 1972 to 1982 stroke deaths declined by 42 percent and heart disease fatalities were down 27 percent. (See accompanying chart.)

High blood pressure is the major risk factor for, or cause of, strokes. It is one of the three main risk factors (along with cigarette smoking and high cholesterol levels in the blood) for heart attack. Stroke and heart disease are not only deadly and debilitating diseases but they are also expensive, costing the nation more than \$60 billion each year.

Blood pressure is measured in two numbers, such as 120/80 (120 over 80). The first number, called the systolic blood pressure, is the measure of the force of the blood against the walls of the arteries when the heart pumps. The second number, the diastolic blood pressure, is the pressure remaining in the arteries between heartbeats.

High blood pressure is generally considered to start at 140 and 90.

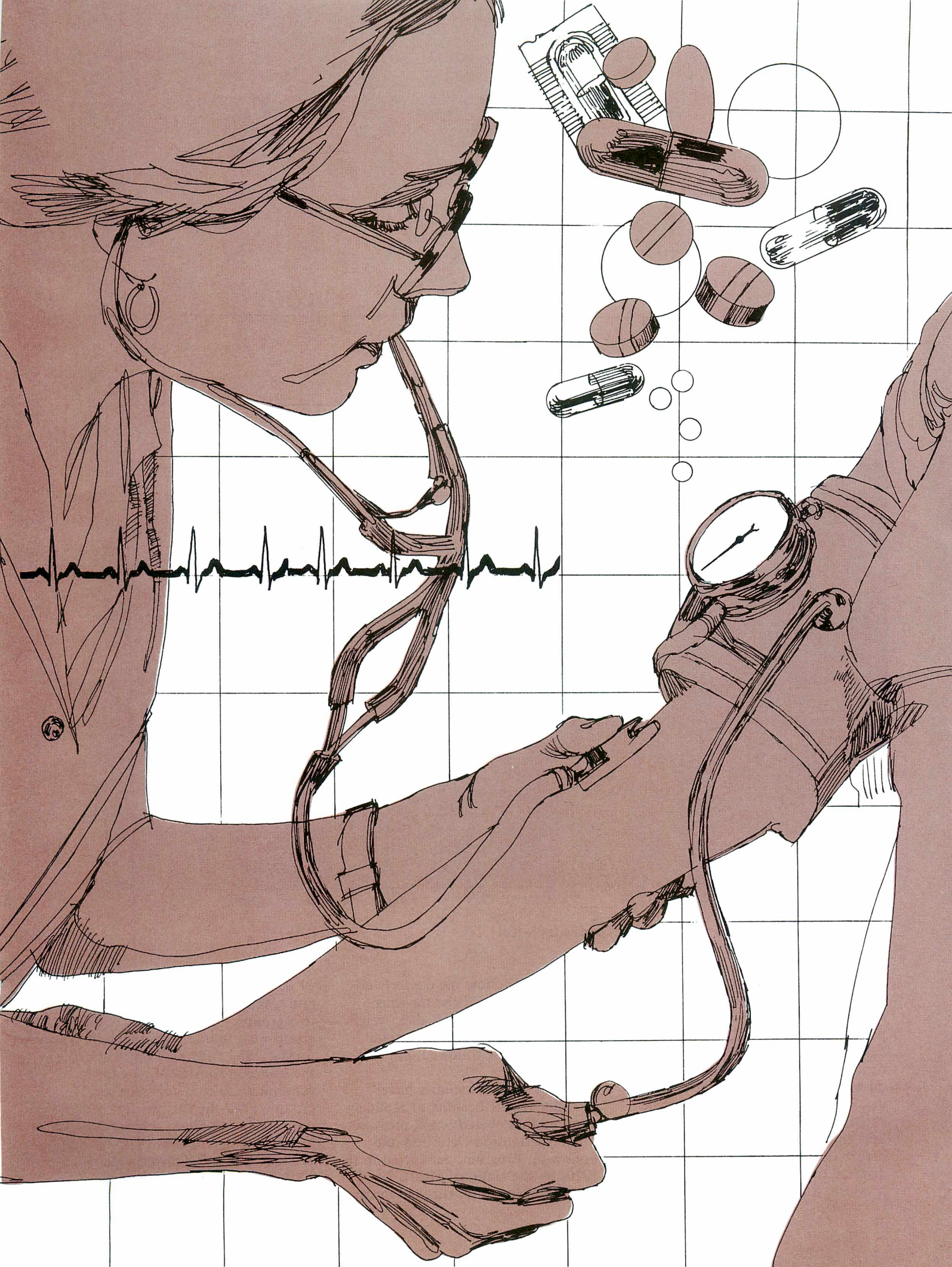
Very seldom does high blood pressure, or hypertension (they mean the same), show itself in the form of symptoms. A person who has high blood pressure will not feel ill and so may not seek medical attention because of it. With unfortunate frequency he or she finds out that

disaster was impending only after suffering a stroke or heart attack.

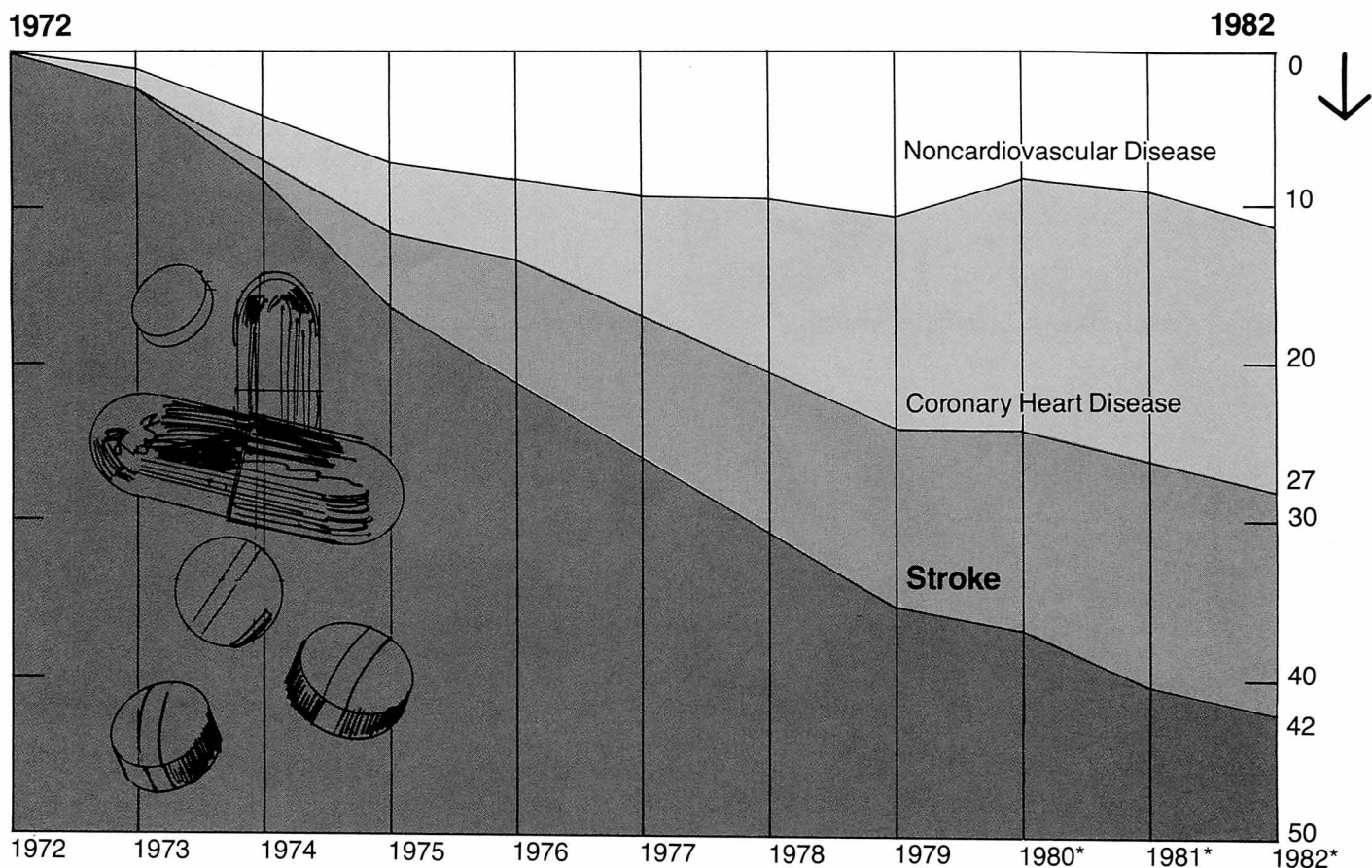
Hypertension is easily detected by a standard blood pressure testing device and, once discovered, can be treated effectively in most cases. An individual's blood pressure is measured by fitting the device's inflatable cuff around the patient's upper arm and listening through a stethoscope. One measurement of elevated blood pressure does not confirm a diagnosis of high blood pressure, but continuing high readings during two or more visits to the doctor's office are evidence that treatment should be started to bring down the pressure.

Many people can reduce their high blood pressure simply by losing weight (if they are overweight) and exercising, especially if the blood pressure is only a little elevated. If those measures don't work or if the blood pressure is elevated dangerously, drug therapy should be started. For treatment of hypertension, a large number of drugs are available, giving the physician a choice while taking into account a patient's needs, lifestyle, allergies and so forth. Also, physicians have learned to give an individual drug in a low to moderate dosage to avoid side effects. If a single drug is not effective in controlling hypertension, a second drug is added to the treatment schedule, also in a low dose. By keeping any drug in as low a dose as appropriate, the doctor generally can prevent or minimize side effects. (For a list of drugs used to treat hypertension, see "The Story Behind Those High Blood Pressure Readings" in the May 1981 *FDA Consumer*.)

The main problem in controlling high blood pressure is getting patients to stay on treatment. Many people find it hard to accept the need to take



Percent of Mortality Decline



*Provisional Rates Published by NCHS and Rates Estimated by NHLBI

a pill every day to treat a condition that they can't tell they have. People tend to drop treatments or to take the pill when they feel bad or have a headache in the mistaken belief that their high blood pressure is bringing on whatever symptoms they're feeling. High blood pressure cannot be cured. Treatment is almost always for life, and the individual needs to realize that. If a doctor puts an individual on a drug for high blood pressure, that individual must stay on

therapy and follow the doctor's advice to the letter. If the treatment program involves drugs, diet, weight control and/or exercise, the total therapy must be followed, not just part of it.

Recent scientific studies have brought out the benefits of reducing even mildly elevated blood pressure. The Hypertension Detection and Follow-up Program, conducted in the 1970s by the National Heart, Lung and Blood Institute, enrolled nearly

11,000 persons in the United States and Canada and divided them into two groups. The volunteers in one group were told they had high blood pressure and then were sent back to their normal sources of care in the community. Those in the second group, called the stepped-care group, were treated to attain a specific blood pressure goal. For those with a diastolic (the low number) reading of 100 or more, the goal was to get down to 90. For those whose blood

pressure was between 90 and 99, the goal was to reduce the reading by 10 millimeters of mercury.

After five years, the individuals referred to their doctors had made progress, but not nearly so much as those in the stepped-care group. This group ended up with 17 percent fewer deaths overall than did those in the referred-care group—7.7 percent of the patients in the referred-care group died during the study, versus 6.4 percent in the stepped-care group, a significant difference. The results were even more pronounced among those individuals with only mildly elevated blood pressure (defined for the study as a diastolic pressure between 90 and 104). The difference between the groups in this range was a 20 percent greater reduction in deaths among the stepped-care patients.

When the investigators looked only at strokes, both fatal and nonfatal, an even more encouraging trend was found. Stroke deaths were reduced in both groups, but the stepped-care group had 34.5 percent fewer stroke deaths than did the referred-care group. Another dramatic finding was that black women in the stepped-care group experienced 45.5 percent fewer stroke deaths compared with black women in the referred-care group. Reduction of blood pressure was most beneficial to those persons whose beginning diastolic blood pressure was in the upper stratum (over 115). Those in the stepped-care group had 45 percent fewer stroke deaths than did the other group. No matter how the investigators divided the groups—by age, by sex, by race, by entry blood pressure, and so forth—the individuals in the stepped-care group fared better than those in the referred-care group. The overall conclusion of the study was that the systematic, effective control of high blood pressure has great potential for

reducing deaths significantly among hypertensives, including those who have only “mild” hypertension.

As increasing public awareness of high blood pressure leads to better control of the disease, stroke deaths no doubt will continue to drop. Only within the past 10 or 15 years has hypertension been the subject of a concerted national effort to alert the public to the dangers of high blood pressure and the necessity to take steps to control it. Some three decades ago, many in the medical profession regarded high blood pressure as nature's mechanism to compensate for hardening of the arteries to insure an adequate flow of blood to the body organs such as the brain and kidneys. It was not until the late 1960s that a study reported by the Veterans Administration clearly demonstrated the value of treating high blood pressure. It was these studies that helped stimulate the beginnings of the national education program.

In 1972, Elliot Richardson, secretary of the Department of Health, Education, and Welfare, directed the National Heart and Lung Institute (now the National Heart, Lung and Blood Institute) to begin a far-reaching program to increase public awareness of the dangers of high blood pressure and to inform the medical profession of the benefits to be gained by lowering elevated blood pressure. The American Heart Association, the American Medical Association, and the National Medical Association joined the institute in launching the new program. Today more than 30 organizations are represented on the Coordinating Committee of the National High Blood Pressure Education Program. The overall effort includes 150 national organizations, business and labor, and many agencies at all levels of government,

including each state health department and approximately 2,000 community-based programs.

A survey, carried out at the time the public education program was initiated, revealed that nearly half of those with high blood pressure were not aware that they had it. The same survey, repeated from 1976 to 1980, showed that the percentage of people who had high blood pressure but were not aware of it had been reduced to 26.6 percent. The surveys also found that the percentage of hypertensives who were controlling their blood pressure had more than doubled over the past decade. Furthermore, several studies show a significant increase in the past decade in public knowledge of the link between stroke and high blood pressure. For example, in 1973 only 29 percent of the respondents in a survey were aware that high blood pressure can cause strokes. By 1982 this increased to 66 percent.

The success of the public education program is at least partially reflected in the decline in deaths attributed to strokes and heart disease. The efforts to increase awareness of high blood pressure and its dangers continues. Ultimately, however, it is the individual's decision to keep checking his or her blood pressure and, if hypertension is present, to stick to whatever treatment program is established by a doctor.

More information on high blood pressure can be obtained by writing to the National High Blood Pressure Information Center, 120/80, Bethesda, Md. 20205.

Larry Blaser is chief of the Research and Reporting Section, Public Inquiries and Reports Branch, National Heart, Lung and Blood Institute.

NO Menstruation, Pregnancy = AMENORRHEA

by Carol Ballentine

JANUARY 1984							FEBRUARY 1984							MARCH 1984						
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She knew she couldn't be pregnant. But she had missed three menstrual periods and, even though she felt healthy, she was beginning to wonder if something was wrong. Then she read an article in a magazine that said amenorrhea (failure to menstruate) was common among female runners. Since she had just taken up jogging six months earlier, she decided this must be the cause of her sudden irregularity. A month later she got her period and thought no more of it.

This jogger may or may not have had the right solution. Menstruation is a finely tuned physiological process, subject to many influences, internal and external. It is not uncommon for a woman occasionally to miss a menstrual period.

It's more unusual and of more concern for a woman to stop menstruating for three months or more, or never to begin at all. This condition is called amenorrhea (a = without; men is from the Greek for month; and rhea = flow, or discharge). A girl who doesn't start menstruating in her teens (usually by 16 to 18, according to most texts)

is said to have primary amenorrhea. When menstruation stops after it has begun, the condition is called secondary amenorrhea.

The menstrual cycle involves a number of the body's organs and hormones in a process that stretches the length of the body. The cue to menstruate might be said to start in the brain in an area called the hypothalamus, which at the appropriate time each month releases a hormone called GnRH (which stands for gonadotropin releasing hormone). This causes the pituitary gland, a pea-sized organ attached to the hypothalamus, to release the so-called gonadotropic hormones, LH (luteinizing hormone) and FSH (follicle stimulating hormone). (See "The Pituitary: A Kernel Of Wonder" in the February 1984 *FDA Consumer*.)

LH and FSH then stimulate one (or sometimes both) of the ovaries to mature and—in the process called ovulation—produce ova, or eggs, ready to be fertilized. LH and FSH also cause the ovaries to secrete the hormones estrogen and progesterone. The quantity and order in

which these hormones are released control the development of the endometrium (the lining of the uterus), which thickens each month to provide a "home" for a fertilized ovum. If the ovum is not fertilized during its journey to the uterus, this build-up of endometrial material is sloughed off and flows out of the body through the cervix and vagina in the process called menstruation.

A dysfunction at any point can cause menstrual problems, including amenorrhea. For example, a girl who has no vagina will not menstruate. Although this may seem unlikely, it is a relatively common cause of primary amenorrhea. Approximately 12 percent of patients with primary amenorrhea will have this condition, in which the vagina is either absent or in a state of arrested growth.

The most common causes of primary amenorrhea are in-born defects of the uterus, ovaries or vagina that are caused by chromosomal abnormalities. One of these is testicular feminization syndrome (also called pseudohermaphroditism), in which a child who appears to be a girl actually is a boy—that is, the chromosomes are XY instead of XX. Such children have normal female genitals but only a partially developed vagina and no uterus. They also have underdeveloped testes that may go unnoticed until a close examination is made.

Another condition traced to chromosomal abnormality is Turner's syndrome, caused by complete or partial absence in the female of one of the two X chromosomes. Girls with this condition have underdeveloped ovaries incapable of developing ova—or of secreting the hormones necessary to maintain the menstrual cycle.

Although primary amenorrhea is most often caused by genetic abnormalities and the resulting defects in the sexual organs, secondary amenorrhea usually has its roots in what is known as the hypothalamic-pituitary-ovarian axis (HPO axis). The HPO axis is the brain-to-ovaries communication, carried out by the various hormones (LH, FSH, estrogen and progesterone). If something disrupts communications, a result can be failure to menstruate.

Many women who complain to their doctors of secondary amenorrhea have polycystic ovary syndrome, in which one or both ovaries enlarge and thicken. It is a consequence of persistent anovulation (failure to ovulate), which eventually manifests itself as amenorrhea. Since there are many causes of anovulation—most rooted in the hypothalamus and pituitary—there are also many types of polycystic ovaries. Other symptoms of polycystic ovary syndrome are obesity, infertility and hirsutism (abnormal growth of hair), particularly on the face.

Anovulation can be caused by tumors of the pituitary gland, called adenomas, which are responsible for about a third of all secondary amenorrhea cases. The most common is the prolactin-secreting tumor.

Prolactin, secreted by the pituitary gland, stimulates the secretion of breast milk. This hormone is released in response to suckling (as nerve signals from the breasts

travel to the hypothalamus, which in turn sends its signal to the pituitary gland). Excessive prolactin can cause both amenorrhea and anovulation. That's why some 50 percent of nursing mothers do not menstruate. A prolactin-secreting pituitary tumor can cause the inappropriate release of excessive prolactin, a condition called hyperprolactinemia.

Ordinary menstrual irregularities are frequently caused by physical and mental stresses that throw the hypothalamus slightly out of adjustment, but sometimes these same stresses can also lead to amenorrhea. Located in the center of the brain, the hypothalamus might be considered as an information processing center, both receiving and sending signals vital to the body. As part of the nervous system, it is sensitive to stimuli collected through the five senses. It also stimulates release from the pituitary of hormones that control many of the body's functions (including eating, sleeping, and sexual activities).

Travel, change in climate or sleep habits, and mental distress all can affect menstrual regularity. If the stresses are great enough, the clinical condition of amenorrhea can be the result. Dr. Hilde Bruch, professor of psychiatry at Baylor College of Medicine in Houston, says in her book *Eating Disorders*, that "amenorrhea is commonly observed in women under severe stress and strain Under wartime conditions, in concentration and internment camps, incidence of amenorrhea was high" Likewise, women with mental problems such as those in mental institutions can lose their menstrual cycles.

Hypothalamic amenorrhea also can be caused by acute loss of weight, as may occur in crash dieting. Dr. Rose E. Frisch, of the Harvard Center for Population Studies, Cambridge, Mass., holds that regular menstrual periods depend on the maintenance of minimum weight to height. She says amenorrhea results from a loss of about 10 to 15 percent of body weight (about one-third of body fat).

There is some evidence that loss of body fat leads to dysfunction of the hypothalamus and subsequent reduction in FSH and LH, which in turn causes failure to ovulate. Frisch claims this is an adaptive mechanism that prevents a woman from having a baby if she hasn't enough calories to nurture the fetus; not all authorities agree with this theory.

Amenorrhea is a common symptom of anorexia nervosa, a psychiatric disease characterized by aversion to eating and extreme weight loss. Patients with this condition—usually adolescents and women in their early twenties—suffer from unrealistic concerns about gaining weight and about how they look. Even when emaciated to a point requiring hospitalization, victims frequently insist that they are "too fat."

Most medical experts say that the weight loss in anorexia causes the amenorrhea. Some claim, however, that the amenorrhea in such patients precedes the weight loss. They believe an abnormality in the hypothalamus causes

both the disease and the loss of menstrual periods.

Another cause of hypothalamic amenorrhea consistent with weight loss is strenuous physical activity. Dr. Phil Price, gynecologist with FDA's Center for Drugs and Biologics, says amenorrhea is occurring more frequently now in women who run long distances, as in marathons. He notes, however, that it doesn't seem to become a problem until a woman begins running about 20 miles a week or more, and even then it won't necessarily occur.

The author of one gynecology text, Dr. Leon Speroff, says that young women who weigh less than 115 pounds and lose more than 10 pounds while exercising are most likely to develop amenorrhea. One reason, Speroff says, is the loss of body fat, female athletic competitors having about 50 percent less body fat than noncompetitors. Another reason is stress and expenditure of energy, which seem to contribute to hypothalamic dysfunction. For instance, in one study researchers found that dancers who are amenorrheic during their professional season will often resume menstruating during intervals of rest.

Speroff adds, "The magnitude of the problem of exercise and amenorrhea has changed considerably in the last decade. In the early 1970s, a woman jogger was a curiosity. Today, millions of women are running, over a million girls play soccer, and more than a third of high school athletes are female."

Some drugs can also throw the menstrual mechanism out of whack, although this adverse reaction is not commonly reported. FDA's Annual Adverse Reaction Summary Listing includes 324 cases of drug-related amenorrhea from 1969 to 1983. The drugs heading the list were antipsychotics (especially the phenothiazines) and oral contraceptives.

Antipsychotic drugs, which are used to treat schizophrenia and other psychiatric conditions, may cause hyperprolactinemia (excessive production of prolactin by the pituitary). That can lead to amenorrhea. Thioridazine (brand name Mellaril) is particularly known to cause this problem.

Medical opinion differs about the relationship of oral contraceptives to amenorrhea. Many medical texts, including *The Merck Manual* and the American Pharmaceutical Association's *Handbook of Nonprescription Drugs*, say that discontinuing use of oral contraceptives is a common cause of amenorrhea.

The American Medical Association, however, in its reference book *AMA Drug Evaluations* (5th edition), says, "Whether a causal relationship exists between use of OCs [oral contraceptives] and subsequent amenorrhea is unresolved. In most studies, this effect is reported in less than 1 percent of patients who take OCs. The incidence of spontaneous secondary amenorrhea in women who do not take OCs is similar"

Some diseases can upset the menstrual cycle. Tuberculosis can attack the ovaries or uterus. Nephritis, a

chronic kidney disease whose symptoms include excessive urination, can alter the hormone balance necessary for menstruation (hormones are eliminated from the body through urine). Diseases of the thyroid gland and the adrenal glands—and subsequent over- or underproduction of hormones by these organs—can also cause amenorrhea.

In treating amenorrhea, the cause must first be identified. In most cases a doctor can do this by using hormones, such as progesterone, in a series of tests.

In primary amenorrhea, menstruation can be induced with progesterone, and hormone therapy (usually estrogens or estrogen and progesterone) can be started to aid in development of secondary sex characteristics (such as development of breasts and pubic hair).

For patients with secondary amenorrhea, treatment depends both on its cause and the patient's goals. If a woman wants to become pregnant, the doctor might prescribe drugs to restore fertility. Bromocriptine mesylate (brand name Parlodel), a prescription drug that inhibits secretion of prolactin and causes pituitary tumors to shrink, is used to correct amenorrhea and infertility resulting from hyperprolactinemia. Another prescription drug, clomiphene citrate (Clomid and Serophene), can stimulate ovulation by increasing secretion of GnRH. This raises levels of FSH and LH so they are sufficient to stimulate the ovaries. (See "Infertility And How It's Treated" in the June 1983 *FDA Consumer*.)

If pregnancy is not a goal, treatment with progestin may be used to restore the menstrual cycle. This is recommended by *AMA Drug Evaluations* to prevent endometrial hyperplasia (abnormal thickening of the lining of the uterus). If untreated, endometrial hyperplasia can progress to endometrial cancer.

One woman out of 100 will get amenorrhea at some time in life; many more will skip a period or two or experience some type of menstrual irregularity. Should a woman who misses several periods simply wait for her cycle to resume, assuming that if she feels healthy nothing is wrong?

Maybe—if she is running over 20 miles a week, says FDA's Dr. Price. Dr. Joan Ulliyot, author of *Running Free*, advises women runners not to worry about amenorrhea. Ulliyot says that menstrual irregularity, "probably the single most important concern among women runners," is common among healthy runners and does not mean that something is wrong physically.

Dr. Price says for a woman who is not a jogger and who is not pregnant or on birth control pills, amenorrhea can indeed be a warning that something in the body, such as the hormones, has gone awry. Price says such women who have missed more than two periods should be checked by their doctors.

Carol Ballentine is a member of FDA's publications staff.

Most M.D.s Keep *The Merck Manual* Handy (Some Mothers Do, Too)

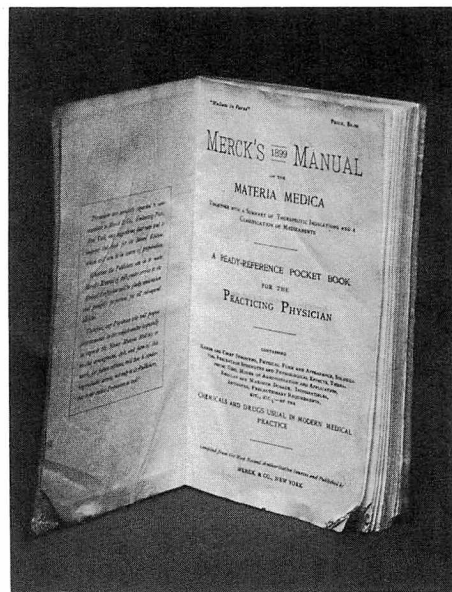
by Evelyn Zamula

To Whom It May Concern:

I just wanted to share my story with you in regard to using my Merck Manual. I'm a registered nurse with 15 years clinical nursing experience. Last week, because I had my Merck Manual in easy reach, it helped me recognize what was happening with my 11-year-old daughter. I had a suspicion that she was getting "epiglottitis"—but upon referring to my Merck Manual I was sure. It gave me the precise quick information which led me to seek medical information and saved her life

My daughter was critically ill—but is recovering nicely. The book gave me insight into how they (doctors) would treat this condition The nightmare of this disease would have been tragic if I hadn't had my Merck Manual to refer to.

Thanks for publishing such an informative book.



The book that helped this mother out in a crisis is *The Merck Manual of Diagnosis and Therapy*, published by Merck Sharp & Dohme, the pharmaceutical division of Merck & Co., one of the giants of the drug industry. The current editor-in-chief is Dr. Robert Berkow, a specialist in internal and psychosomatic medicine.

Dr. Berkow's files are full of similar letters from grateful users, both from medical personnel and nonprofessionals alike. But, though laymen consult the book, it was never intended for them—the language is too technical for the average person. The manual's primary purpose, according to the editor, is to "provide useful information to practicing physicians, medical students, interns, residents and other health professionals." Dr. Berkow recommends

that any person contemplating buying the book examine it first.

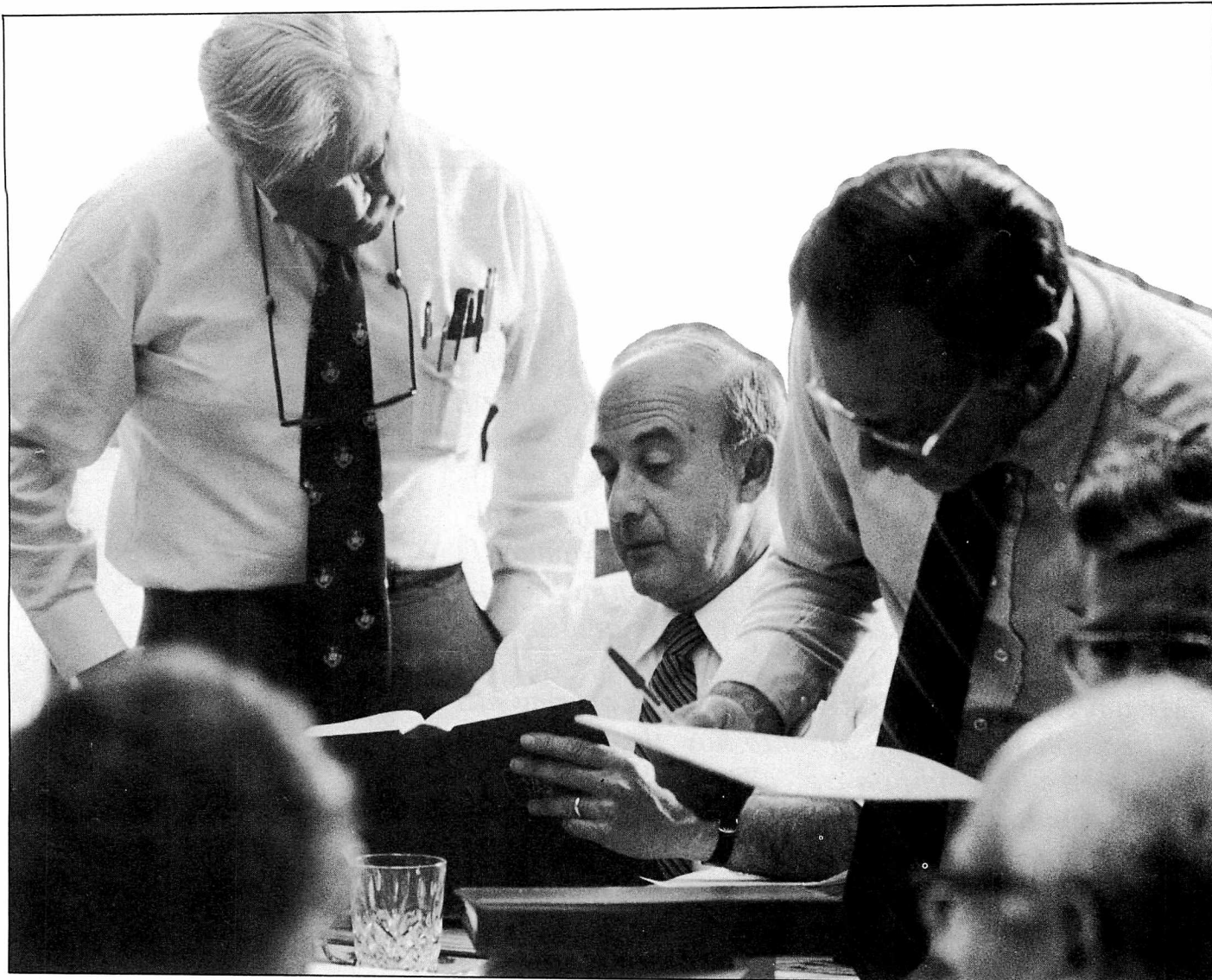
Consider the symptoms and signs for that age-old affliction, indigestion: "Belching, abdominal distention, and borborygmus are often described in addition to epigastric or substernal pain. Eating may worsen or relieve the pain. Other associated symptoms may include anorexia, nausea, and change in bowel habits. Dysphoric states such as anxiety or depression may be found." There are just enough familiar words to make the condition understandable to most people, but borborygmus?

Difficult language or no, the book sells. The 13th edition, which came out in 1977, sold 800,000 copies; the current 14th, published in 1982, is selling even better so far. The manual has been translated into Spanish and

German, and more translations are in the works. It is the most popular medical reference book in the world. Many public libraries stock it, often under lock and key, because some readers like it so well it's hard to keep the book from disappearing.

Recently it has traveled with the Peace Corps all over the world, and earlier accompanied Albert Schweitzer into the African jungle. It is used on military posts and on shipboard, and has been stashed in the fallout shelters of those who hope to survive an atomic war. It is often the mother's helper and the hypochondriac's bible.

The most recent manual, of about 2,600 pages, is a far cry from the first edition of one-tenth its size, published in 1899. Translated from the German, this little book, titled *Merck's Manual*, listed well over 900 remedies



Members of The Merck Manual editorial board are (left to right) Dr. Robert G. Petersdorf, dean of the University of California in San Diego School of Medicine; Dr. Robert Berkow, editor-in-chief; and Dr. Alvan R. Feinstein, professor of medicine and epidemiology, Yale University.

Photos courtesy of Merck Sharp & Dohme.

alphabetically, mostly chemical compounds and natural products, and what they were good for. It also described disease symptoms, followed by every known or possible treatment. Another section of the book classified the remedies according to their function (e.g., digestives, purgatives).

Some of the primitive treatments and available drugs in that initial edition are laughable today. Bloodletting was still recommended for disorders

such as insomnia, pleurisy, sunstroke, headache and psoriasis, among others. For those Victorian times, a surprising number of sexual disorders were described. Fifteen cures were noted for nymphomania, one being tobacco to cause nausea. The manual recommended arsenic, rarely used in any therapy today, for more than 100 diseases, including jaundice, hydrophobia, elephantiasis and impotence. Belladonna, iodine, cannabis indica and eucalyptol were widely used.

There were 75 possible remedies listed for diphtheria, 96 for gonorrhea, and 68 for diabetes mellitus. The less that was known about a disease, notes Dr. Berkow, the more remedies were listed for it.

But it won't do to laugh too much at what is considered ridiculous now, as Dr. Harold J. Morowitz, professor of molecular biophysics and master of Pierson College at Yale, pointed out in *Hospital Practice* magazine (December 1976): "It is easy to sit

back and chuckle at our predecessors. Hindsight is a most effective tool. But I think amusement alone would be a poor use to make of the 1899 *Manual*. The practitioners of that era were no less dedicated and considered themselves no less educated than those of today . . . We might project ourselves 77 years into the future and envision some curiously perverted prose writer thumbing through a yellowed, cracking 12th edition of *The Merck Manual*. Surely he too will have a few laughs and wonder how ineffectual was the physician of 1976."

The first edition may have been hopelessly antiquated according to our lights, but it was a big hit with the medical profession. At last the physician had a practical reference tool that could refresh his memory and "enable him to prescribe exactly what his judgment tells him is needed for the occasion," says its introductory pages. The book was notable for another reason: It was the first and last edition that was free. And it wasn't shy about plugging Merck's products.

With the second edition, Merck & Co. began marketing the manual at cost purely as a service to the medical profession; and the book gained in dignity when the commercials were dropped with the fourth edition. The company's products had become well known, and Merck was achieving a reputation as a publisher of authoritative reference materials. (Merck also publishes *The Merck Index*, an encyclopedia of chemicals and drugs begun in 1889, and started up *The Merck Veterinary Manual* in 1955.)

The eighth edition of *The Merck Manual* was a milestone issue. Appearing in 1950 after a 10-year hiatus, it represented a sharp break with the past. It reflected the tremendous medical progress made in the previous decade—partly a result of the knowledge gleaned from World War II experiences, and partly due to the discovery of antibiotics and the sweeping advances in organic chemistry. It also had a new editor, Dr. Charles E. Lyght, and a new title. Dr. Lyght gave the book its present name, rearranged it into logically related groups, added a section of how-to-do-it advice on clinical pro-

cedures and other subjects, and greatly expanded the subject index, which had appeared first in the seventh edition.

The book's format has held steady ever since. The latest edition is organized mainly according to diseases of certain organs (heart, liver, kidney, etc.), their causes (by bacteria, viruses, or physical agents such as heat, cold or sunlight, etc.), and medical specialties (obstetrics and gynecology, psychiatry, etc.). In addition, there is a long chapter on clinical pharmacology that discusses drugs and how they act in the body. The emphasis throughout is on diagnosis and treatment.

The manual offers comprehensive and accurate information on the whole range of medical disorders that afflicts mankind. It covers all but the most obscure diseases, and describes each disease or pathological condition in detail, with causes, symptoms and signs, treatment, and possible outcome. It also recommends the tests necessary to diagnose a condition.

Special attention is given to the problems of pregnancy and delivery and the more common and serious disorders of newborns, infants and children. A chapter is devoted to dental and oral disorders. Complicated medical devices, such as dialyzers and respirators, used in treating patients are described.

It discusses some medical emergencies that most physicians never encounter in a lifetime—how to treat "the bends," for example, or overexposure to radiation from a nuclear power generator, or mushroom poisoning. Nor is the increasing interaction of medicine and the law omitted: The section on rape tells the doctor how to prepare the medical record and collect specimens, because these often become evidence in the courts. It even advises when and how to prescribe a placebo.

Making sure that the text stays up-to-date is a challenging job, considering the fast pace of medical discovery. The current edition includes both new or previously unidentified diseases (Legionnaires' disease, toxic shock syndrome) and new therapies. It describes the latest clinical and laboratory procedures and the most sophisticated technologies, such as

CAT scans, ultrasound, and radioisotope imaging, with comments on their uses and limitations. The upcoming 15th edition, scheduled for 1987, will contain information on acquired immune deficiency syndrome (AIDS), nuclear magnetic resonance systems (NMRs), and a whole new discussion of cancer.

It hardly needs saying that the writers of the articles—all 272 of them—are tops in their fields. Most are professors, chairmen of departments at leading medical schools, or heads of hospital specialty units. The majority of the authors are in the United States, but contributions also come from Canada, Israel, South Africa, England, Scotland and France.

No sooner is one edition off the press than work on the next one begins. The editor and his staff read every critique of the previous edition and analyze every piece of correspondence, whether from the medical profession or from the public.

The biggest problem is keeping the book at a comfortable size. As the body of medical knowledge grows, the book tends to put on weight. To pack as much information as possible into the manual while keeping it trim, manuscripts are usually revised at least a half dozen times, according to editor Berkow, and 15 to 20 revisions are not uncommon. He adds that some manuscripts take as long as 18 months to reach finished form.

An editorial board, composed of experts in their fields, reviews the manuscripts. Outside consultants are also called in to resolve differences of opinion.

Besides being an invaluable help in the diagnosis and treatment of disease, *The Merck Manual* may also be regarded as a social chronicle. A quick glance at the index reveals many of the problems that plague our society—abuse and neglect of children, cocaine dependence, contraception for adolescents, teen-age suicide, alcohol and fetal development, sexually transmitted diseases, care of the aged, cigarette smoking.

But the manual points no fingers and preaches no sermons. That's the business of another Bible.

Evelyn Zamula is a member of FDA's publications staff.



Joys Of A-mushrooming

I would like to comment on Evelyn Zamula's fine article "The Mushroom is a Fickle but Yummy Treat," which appeared in the Dec. 1983-Jan. 1984 issue of *FDA Consumer*.

Her article is interesting, well-written, and factually accurate. There is, however, one glaring omission.

Ms. Zamula spends a good deal of time developing the idea that indiscriminate or careless mushroom hunting for the table is very dangerous. I agree wholeheartedly, and I tell people the same thing when discussing the subject. One thing she did not do, though, is mention the fact that there are many classes offered in basic mycology and/or mushroom hunting by universities, colleges, parks and nature centers. There are also many clubs and societies that interested persons could join to learn more about edible (and poisonous) mushrooms.

I taught a class in wild mushroom hunting at a local nature center last fall. I am also a member of the second oldest amateur mushroom hunting club in the United States, the Minnesota Mycological Society.

Mushroom hunting can be as safe as stamp collecting, or it can be one of the most dangerous and foolhardy things a person can do. All one needs to do is take the time to learn the basics of proper identification, and never eat anything that (s)he cannot positively identify. . . .

William Jaspers III
6700 11th Avenue South
Richfield, Minn. 55423

Mr. Jaspers' point is a good one. Those with the wild mushroom bug can find all kinds of activities in their areas. Most basic mycology courses in colleges and universities tend to treat the whole range of fungi, with no particular emphasis on edible mushrooms. Therefore, if food is what you're interested in, it's wise to check with the professor before signing up.

Dr. Kent McKnight, of the U.S. Department of Agriculture's Beltsville (Md.) Agricultural Research Center, recommends contacting the North American Mycological Association for the locations of the 64 affiliated clubs in this country and Canada. The local clubs often give lectures or sponsor courses in wild mushroom identification. Write to:

Harry C. Knighton, Executive Director, NAMA, 4245 Redinger Road, Portsmouth, Ohio 45662.

One such club, the San Francisco Mycological Society, recently played a key role in saving the lives of the 14 Laotian refugees who ate Amanita phalloides last winter—an incident that is thought to be the largest single episode of mushroom poisoning in the United States.

When the first of the Laotians began coming into the Brookside Hospital (San Pablo, Calif.) emergency room, the physician on duty had the good sense to contact the society for help in identifying the mushroom they had eaten. A member of the society went over to the hospital and positively identified a portion of a cap as Amanita phalloides. The doctor chairing the society's toxicology committee also was asked to recommend possible therapies.

Since about 30 hours had elapsed since they had consumed a rice, meat and mushroom stew, too late to pump stomachs, all patients received supportive care, including the introduction of a charcoal-saline solution slurry to the intestines to reduce absorption of the amatoxins. Although some of the victims were near death, all survived.

The victims thought they were eating a larger version of the sheathed Paddy Straw mushroom, common in southeast Asia. Dr. McKnight notes that most cases of mushroom poisoning occur among immigrants or their children, who think that what they're picking is the same as an edible variety grown in the old country.

Correction

FDA Consumer has been advised that the information regarding the indications for use of naproxen (Naprosyn) and naproxen sodium (Anaprox) in the article "For Treating Arthritis, Start With Aspirin" (*FDA Consumer*, December 1983-January 1984) is out of date.

The current indications for these drugs are: "for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis and bursitis, and acute gout."

In addition, juvenile rheumatoid arthritis has been deleted from the product labeling, pending submission of another controlled study. Therefore, the reference to an indication for treatment of juvenile arthritis is not appropriate for naproxen at this time.

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 large public libraries.

■ FDA denied requests for a hearing on certain safety issues related to the use of **aspartame** in carbonated beverages and carbonated beverage syrups. Two parties contended that decomposition and reaction products were created by the addition of the artificial sweetener to the beverages. The agency concluded that these objections did not raise issues of material fact that justified granting a hearing (FR Feb. 22).

■ March 8 marked the signing of a memorandum of understanding between FDA and the Board of Customs of the Republic of **Finland**. The agreement provides for inspection and certification of Finnish food products before export to the United States and for mutual sharing of inspection information and expertise. The ceremony, attended by about 300 people, was a major event for both the Finnish government and the food industry.

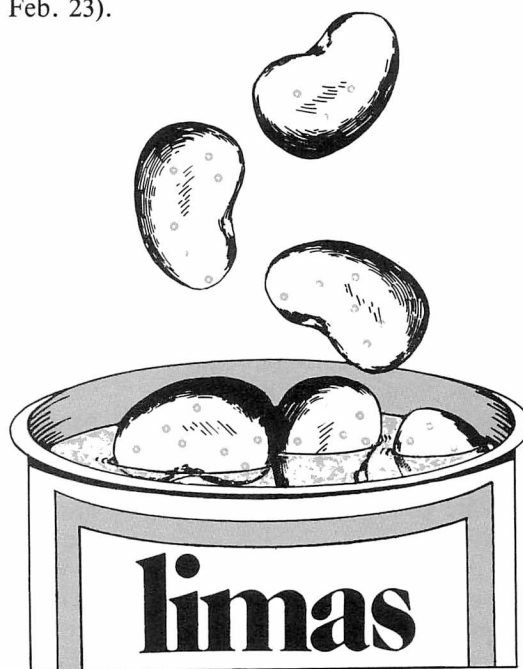
■ Two **alpha-fetoprotein (AFP) test kits** have been approved by FDA. Both AFP-TEST (Farr Technique), made by Wampole Laboratories, and the Quantitope 125-I-AFP RIA Kit, made by Kallestad Laboratories, are used to aid in the detection of fetal open neural tube defects (FR Feb. 17).

■ Beginning Aug. 13, any preparation that contains more than 75 milligrams of the antihistamine **diphenhydramine hydrochloride** in a single package and in a dosage form intended for oral administration must be in a child-resistant package, under a final rule issued by the Consumer Product Safety Commission. At the same time, the commission proposed to broaden this rule to require child-resistant packaging for preparations containing more than 66 milligrams of diphenhydramine in any form or application (FR Feb. 15).

■ **Diabetic** customers spend more in pharmacies than non-diabetics, according to a survey by *Drug Store News*. On an average, the diabetic spends \$100 annually for insulin, \$320 for non-insulin drugs, \$200 for testing materials and related items, and \$75 for syringes. An average transaction costs the diabetic patient about \$30 compared to \$13 for the non-diabetic.

■ The closing date for the provisional listing of **FD&C Yellow No. 6** for use as a color additive in food, drugs and cosmetics was postponed until April 30. This allowed FDA time to review the scientific and legal aspects of the results of toxicological studies submitted by several petitioners (FR Feb. 28).

■ July 1, 1985, is the effective date of a new FDA rule permitting the use of **calcium salts** as firming agents in canned bean sprouts, lima beans, carrots, green sweet peppers, red sweet peppers and potatoes (FR Feb. 23).



■ There will be no U.S. standards based on international standards for **quick-frozen brussels sprouts**, cauliflower, green beans, wax beans, corn on the cob, whole kernel corn, broccoli, and french fried potatoes. FDA says there is a lack of interest and need for such standards (FR Feb. 21).

■ FDA is proposing to affirm that: **copper (cupric) gluconate** and copper (cupric) sulfate are generally recognized as safe (GRAS) as direct human food ingredients; that cuprous iodide is GRAS with specific limitations when used as a source of dietary iodine in table salt; and that peptonized copper is not GRAS (FR Feb. 1).

■ Roquette Corp. has asked that **hydrogenated glucose syrup** be considered GRAS for use in candy, chewing gum and confections (FR Feb. 27).



Investigators' Reports

PMS 'Cure' Sidetracked

by Carolyn Hommel

Not so long ago a woman suffering from premenstrual syndrome (PMS) might have been told her problems were all in her head. Today PMS is generally accepted as a genuine clinical entity. And the symptoms some women experience for one or two weeks during their menstrual cycles (water retention, abdominal pain and cramping, breast tenderness, headache, fatigue, irritability, depression, tension and anxiety) are only too real. (See "Doing Something About 'The Curse'" in the June 1983 issue of this magazine.)

One theory that has been suggested to explain the syndrome is that PMS is caused by a deficiency of progesterone. And, the theory goes, the symptoms can be relieved by administering large doses of naturally occurring progesterone from plant sources. Because natural progesterone in an oral form is absorbed by the liver before it can travel to the rest of the body, PMS sufferers are given the substance in suppository form.

There is one hitch: Progesterone suppositories have not been approved in the United States for this purpose. Thus, physicians who prescribe progesterone suppositories, which are made up in local pharmacies, do so on their own responsibility.

Although some physicians applied to FDA for permission to study the use of progesterone suppositories to treat PMS, FDA did not allow the studies to begin because the proposed dosages exceeded 200 milligrams per day, the maximum limit recommended by FDA's Fertility and Maternal Health Advisory Committee. This, however, did not stop one New Hampshire firm from making and marketing progesterone suppositories.

In the summer of 1983 FDA's Boston district office was contacted by an Oregon pharmacist who had received promotional literature from a firm sell-

ing such suppositories. The pharmacist wanted to know if the firm was legitimate.

Since the firm, H & K Pharmaceuticals of Bedford, N.H., was not registered with FDA, agency investigators sought to call on the company to obtain information on who was actually manufacturing the suppositories, together with the marketing history of the product and samples of the labeling and promotional materials.

Visiting the firm was something else again. The company had had four addresses in Massachusetts and two in New Hampshire since May 1981. The investigators eventually were able to talk to the president, James E. Hovey, outside one of the New Hampshire locations.

It seems Hovey had established the "National Center for Premenstrual Syndrome and Menstrual Distress," a nonprofit organization, to sponsor seminars for physicians and patients wishing to learn more about the diagnosis and treatment of PMS. Hovey had operated PMS treatment clinics in New York and Massachusetts.

The investigators learned that H & K Pharmaceuticals had hired a separate company to manufacture the progesterone suppositories and had shipped 22,000 of them in five dosage forms (25, 50, 100, 200 and 400

milligrams) to pharmacies, physicians and patients in at least 18 states between February and June 1983.

Examination of the products revealed that they failed to bear the name and place of business of the manufacturer, packer or distributor. They also lacked "adequate directions for use" by which physicians could properly prescribe and administer the drug. Finally, the firm did not have from FDA an approved New Drug Application, which would allow the drug to be sold, nor an Investigational New Drug Exemption, which would allow the drug to be shipped in interstate commerce for experimental use.

Hovey was informed that FDA considered his progesterone suppositories to be a new drug without an approved New Drug Application, and the product was therefore in violation of the Food, Drug, and Cosmetic Act. He was also warned about further regulatory action FDA could take.

Hovey acknowledged the warning and stated that no further shipments of the suppositories would be made. But that was not quite the end of the story. A few days later it was learned that H & K Pharmaceuticals had shipped several packages, one to a physician in Massachusetts. A check with the physician revealed that the



package contained progesterone suppositories.

The FDA investigators once again contacted Hovey who told them the shipments had possibly been made by one of his family members without his knowledge or consent.

As a result of this investigation Hovey received a "regulatory letter." Such letters are issued when FDA has evidence that a firm has violated the law and the violation warrants initia-

tion of administrative or legal actions such as recall, seizure, injunction or revocation of a license. The regulatory letter commits FDA to take such actions if the violation is not corrected promptly.

H & K Pharmaceuticals is now out of business.

Carolyn Hommel is an FDA consumer affairs officer, formerly located in Boston but now in Atlanta.



Megavitamins = Mega-problems

Everyone needs vitamin D. It helps build strong bones and regulates metabolism of calcium and phosphate in the body. A diet deficient in vitamin D can cause rickets in children and osteomalacia (a bone disease) in adults.

But too much vitamin D can be harmful—which is why FDA's **Brooklyn district** recently sent a regulatory letter to Bioline Lab Inc., Brooklyn. The firm was marketing vitamin D capsules with a labeled potency of 50,000 International Units. The Recommended Daily Allowance for vitamin D for children over 4 and adults is 400 International Units.

Vitamin D is stored in the liver and fat tissues and is fat-soluble. Since it is not readily excreted it can be highly toxic when taken in large doses. Prolonged hypervitaminosis D (the condition caused by taking excessive amounts of vitamin D) in infants can cause mental retardation, slowed physical growth, kidney failure, and death. In adults early symptoms of hypervitaminosis D are loss of appetite, vomiting, diarrhea and headache. Taking repeated doses can eventually cause heart damage, as well as kidney failure and death.

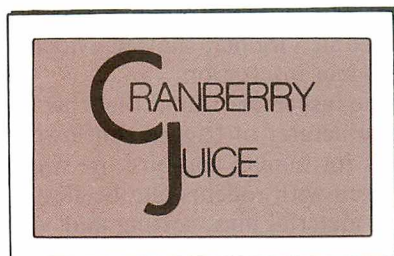
A district investigator visited Bioline to collect a sample of the product. When laboratory analysis confirmed the labeled potency, the district sent a regulatory letter to the firm saying that, at 50,000 International Units, the product was adulterated and potentially hazardous to health.

Representatives of the firm agreed to stop marketing the product. They also recalled 168 bottles from one consignee and sent letters to pharmacists who had been sent three or more bottles, telling them to change the product to prescription status.

Cases Of Odorized Labels

G33 was not a winning number for the Great Northern Juice Co. in Blaisdell, N.Y.

The firm had routinely packaged up single-service plastic cups of cranberry juice for its hospital and



distributor accounts in Pennsylvania, New York and Ohio. The sealed cups hold four ounces each and are packed six dozen cups to a case. Some 500 cases (36,000 cups) were packed with the G33 production code stamped on the tape that sealed each case. Most cases were shipped to Great Northern accounts; a few were put in storage for later shipment.

Within days of shipping, two Buffalo area hospitals reported to the firm and to the Erie County Health Department that there was a strong odor of kerosene or gasoline when the cases of juice were opened. The health officer relayed the report to

FDA's **Buffalo district** office. Meanwhile the FDA office had heard directly from another hospital with the same complaint.

Samples of the packaging and labels from the lot at the hospital were analyzed by FDA's Buffalo laboratory and New York Regional Laboratory. Both found petroleum-based substances that did not belong there. Using mass spectrometry, the New York City lab identified these as aromatic alkyd compounds, similar to lacquer solvent.

New York state and FDA investigators visited the Great Northern plant and found no production problems. They learned, however, that company officials already knew of and thought they had corrected the labeling situation.

It seems that penetrating oil used to lubricate a printing press had gotten onto the ink rollers as Great Northern labels were being printed by Miken Systems of Cheektowaga, N.Y. The labels, now scented as well as printed, were used briefly on the juice production line until an employee noticed the strange odor and replaced them. A dozen cases sealed with the odorous labels were discarded, but several other cases were inadvertently shipped to Great Northern accounts, including the three Buffalo hospitals. There was no health hazard or danger of injury; the oil and odor were on the labels only and did not reach the sealed cups of juice, which were further protected by plastic sleeves.

Realizing that some problem cases must have been shipped, Great Northern decided to recall whatever G33 cranberry juice its customers still

had, including a few packed by Great Northern for a private (Nifda) label.

Back came 46 cases from one distributor, nine from another, and three from one of the hospitals. The other two hospitals had already discarded their cases and been credited by Great Northern.

Several cases were examined and no labeling problems found. Nevertheless, all returned cases of code G33 were dumped, and Great Northern reported that the recall was complete, just three weeks from the time the firm put the labels on.

Still On The Hook

An equipment manufacturer who produced unsafe X-ray units has been told by a federal judge that he cannot escape responsibility by selling his firm and its assets. Neither can he excuse himself by saying he did not personally make the units.

FDA had charged the defendants, Hodges X-Ray Inc. of Louisville and James J. Hodges, the firm's president, with introducing the company's Traceray III diagnostic equipment into interstate commerce when it did not meet the standards of the Radiation Control for Health and Safety Act of 1968.

Evidence indicated that, although the units were unsafe, the firm certified to purchasers that they met federal standards. FDA inspections revealed that some units did not turn off at the preselected time and did not indicate to the operator the exposure time in seconds or pulses. This meant that patients and perhaps operators could be receiving unnecessary radiation from the units.

Because of this hazard, FDA in early 1980 located and seized some 150 Traceray units, all that could be found in the United States. The seizures were necessary because Hodges X-Ray had gone out of business and no longer existed to correct the deficiencies.

FDA sought civil penalties against the firm and its president in the U.S. District Court for the Western District of Kentucky. At a hearing before Judge Charles Allen, the firm claimed that the new holder of the assets was responsible for correcting any deficiencies. The firm's president claimed that he was not

accountable for the firm's past misdeeds.

But Judge Allen disagreed and granted a summary judgment for the government. He ruled that the defendants were guilty of the stated violations involving the 41 units introduced in evidence. Separate penalties of \$20,500 were levied against the firm and its president.

Beyond resolving this particular case, the court ruling is the first judicial statement that corporate officials can be held personally liable for civil penalties under the 1968 radiation health and safety laws.

For The Birds: Sunflower Seeds Diverted

Gourmands of the human and avian species rarely dine on the same delicacies, but sunflower seeds are an exception. Humans consume them as snacks or munchies or as ingredients in baked goods, such as granola bars. Birds like their sunflower seeds neat.

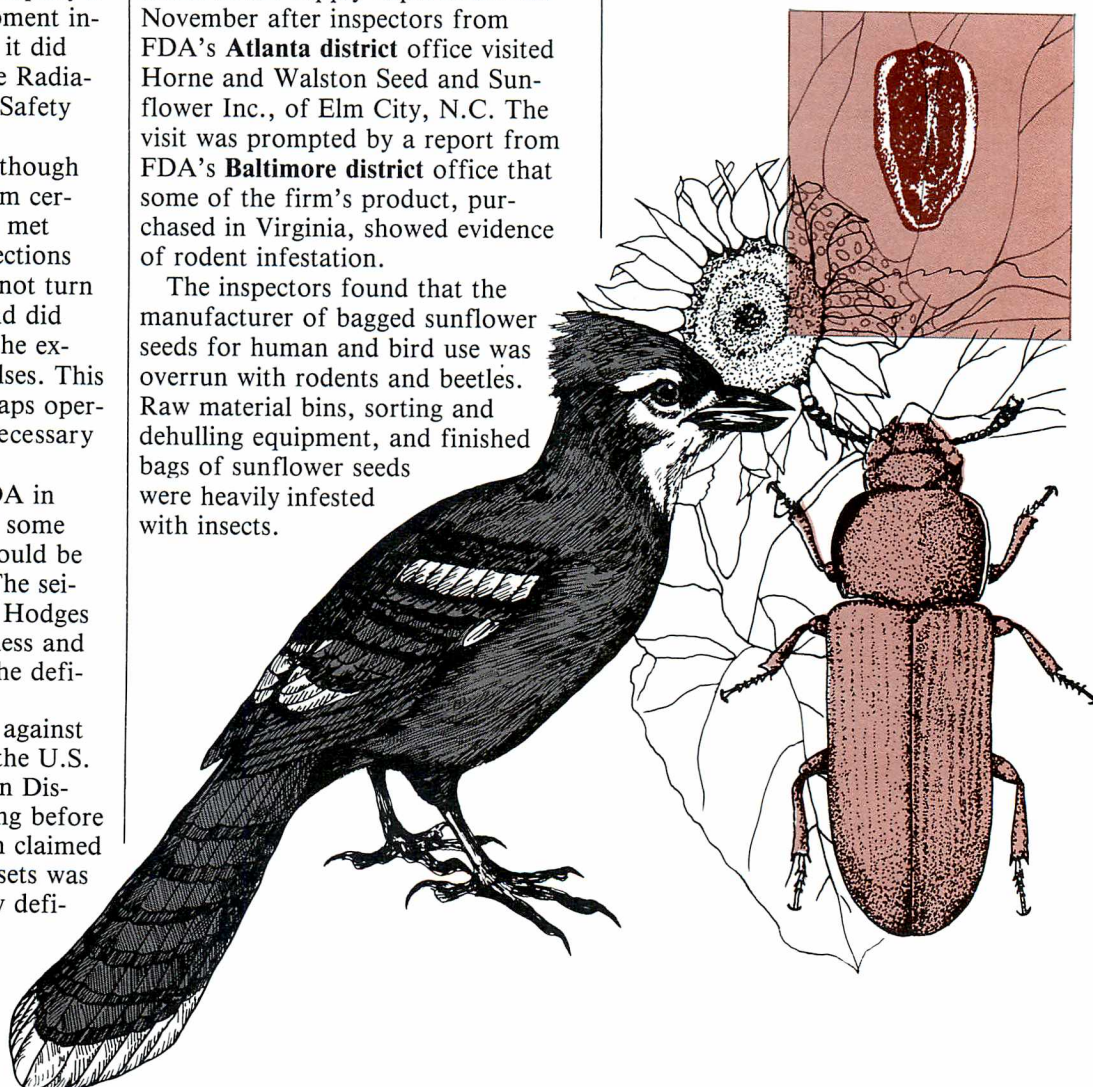
Birds in North Carolina came out ahead in the supply department last November after inspectors from FDA's **Atlanta district** office visited Horne and Walston Seed and Sunflower Inc., of Elm City, N.C. The visit was prompted by a report from FDA's **Baltimore district** office that some of the firm's product, purchased in Virginia, showed evidence of rodent infestation.

The inspectors found that the manufacturer of bagged sunflower seeds for human and bird use was overrun with rodents and beetles. Raw material bins, sorting and dehulling equipment, and finished bags of sunflower seeds were heavily infested with insects.

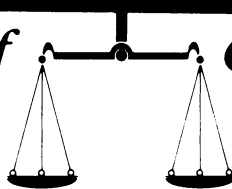
Because all the seed batches in the plant at the time were of local origin and thus were not in interstate commerce, the problem was turned over to the North Carolina Department of Agriculture. The state agency embargoed the entire stock. This was approximately 450,000 pounds of sunflower seeds, including 100,000 pounds in bags awaiting shipment for human use. The state then monitored the fumigation of the premises.

No attempt was made to remove the dead insects from the unhulled sunflower seeds, since these were intended only for feeding birds. The company abandoned efforts to remove insects from the hulled seeds, intended for use in granola bars, after it became apparent that the bags were badly stained with rodent urine. The entire supply of seeds in the plant was thus diverted to nonhuman use.

—This small sample of reports from the field was compiled and edited by Annabel Hecht, Carol Ballentine and Richard Thompson.



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. Full court opinions for these cases are published by either the West Publishing Company or the Commerce Clearing House Inc. Texts can be obtained from Commerce Clearing House at 1301 Pennsylvania Ave., N.W., Washington, D.C. 20004.

Summaries of Court Actions are prepared by the Food and Drug Division, Office of the General Counsel, HHS.

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

SEIZURE ACTIONS

Foods/Contamination, Spoilage, Insanitary Handling

PRODUCT: Cat food and cocoa bean sweepings, at Rochester, W. Dist. N.Y.; Civil No. 79-502.

CHARGED 6-28-79: While held by Specialized Warehouse Enterprises Corp., Rochester, N.Y., the articles contained rodent filth and had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: The dealer claimed the cat food and entered into a consent decree which allowed release of the cat food for salvaging. The cocoa bean sweepings were claimed by Nicholas Merriam, t/a Rochester Steamship Agency, Rochester, N.Y., who claimed that the bags of cocoa bean sweepings had tags that labeled them as "Not for Human Consumption," and that the cocoa beans were not intended for human consumption but that they had considerable value for industrial purposes. On June 10, 1983, after a trial before a U.S. magistrate, the magistrate found that the cocoa beans were adulterated and ordered them to be destroyed. (F.D.C. No. 62368; S. Nos. 79-156-976/7; S.J. No. 1)

PRODUCT: Frog legs, frozen, at Port Newark, Dist. N.J.; Civil No. 82-2563-B.

CHARGED 8-9-82: When shipped by Woolffoods BV, Rotterdam, Holland, the article (labeled in part "Grandtrust Brand Frozen Frog Legs Processed & Packed By: Grandtrust Overseas Pvt. Ltd. Product of India" or "Sun Brand Frog Legs . . . Processed & Packed By: East Coast Fisheries . . . Madras . . . Product of India," and which was a consolidation of a number of lots of frog legs that had previously been refused entry into the United States, returned to Holland, re-containerized, reshipped to the United

States, and again offered for entry) contained the added poisonous and deleterious substance, *Salmonella* microorganisms—402(a)(1).

DISPOSITION: The articles were claimed by the shipper, who stated that through error, accident and inadvertence, the article had not been cleaned and had not had the *Salmonella* removed but had been reexported to the United States without any sanitizing processes having been performed. A consent decree authorized release for salvaging. (F.D.C. No. 63770; Import No. 544507; S.J. No. 2)

PRODUCT: Rawhide bones and rawhide chips for dogs, at Redwood City, N. Dist. Calif.; Civil No. C 82 6439 MHP. **CHARGED** 11-23-82: When imported by Insu Corp., Ltd., San Francisco, Calif., the articles (labeled in part "genuine . . . rawhide bone [or 'chips'] . . . Mr. Max . . . Made In Korea . . . Distributed by: C&L Distributing Co., Mountain View") contained an unidentified deleterious substance in such quantity which might render it injurious to health; and the article was unfit for food due to such substance (household pets had become seriously ill; and in controlled experimental studies, hallucinatory-like reactions in canines had been observed)—402(a)(1), 402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 63877; S. No. 82-345-872 et al.; S.J. No. 3)

PRODUCT: Wheat germ meal, at Orange, C. Dist. Calif.; Civil No. CV 82-6229-AWT(TX).

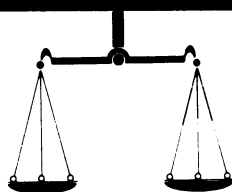
CHARGED 12-1-82: While held for sale, the article contained rodent filth and had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 63915; S. No. 83-259-537; S.J. No. 4)

PRODUCT: Whey, dried, at St. Louis, E. Dist. Mo.; Civil No. 82-2194-C(1).

CHARGED 12-30-82: When shipped by J.M. Swank Co., Inc. (the distributor), Iowa City, Iowa, the article (labeled in part "Krafen Spray Dried Sweet Whey (Edible) Extra Grade . . . Kraft, Inc., Dist., Memphis TN") was unfit for human food by reason of an extremely high aerobic microorganism plate count—402(a)(3); and the article's label was misleading in representing the article to be of human food quality when the article actually was of lesser animal food quality (some portions of the whey failed to meet specifications of the manufacturer for first-quality dried whey for human use. The manufacturer had sold, invoiced, and applied outer labeling tapes to the article directing use of the article for "animal purposes only" but the distributor had removed the outer labeling tapes and sold the article for human food use)—403(a)(1).

DISPOSITION: The article was claimed by the distributor who denied the charges. The government sought and obtained post-seizure samples of the article. Subsequently, a consent decree authorized release of the article to the distributor for bringing into compliance. (F.D.C. No.



63931; S. No. 82-318-923; S.J. No. 5)

Foods/Economic and Labeling Violations

PRODUCT: **Tomatoes, peeled, canned**, at Effingham, Dist. S.C.; Civil No. 82-2918-15.

CHARGED 11-17-82: When returned from Mechanicsville, Va., to McCall Farms, Inc., Effingham, S.C., the quality of the article (labeled in part "Powhatan Brand Peeled Tomatoes Net Wt. 16 oz. (1 LB.) Distributed by Taylor & Sledd, Inc. . . . Richmond, VA.") fell below the standard of quality for canned tomatoes (21 *CFR* 155.90), since the article contained in excess of 1.06 square inches of tomato peel per pound (i.e., contained an average of 3.76 square inches of tomato peel per pound)—403(h)(1).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 63817; S. No. 82-366-221; S.J. No. 6)

Drugs/Human Use

PRODUCT: **Furosemide tablets**, at City of Industry, Cal. Dist. Calif.; Civil Nos. 80-02745-WPG and (upon transfer) CV-81-0263.

CHARGED 7-15-80: When shipped by Superpharm Corp., Central Islip, N.Y., the article (labeled "Goldline furosemide tablets . . . Manufactured by Superpharm Corp., Central Islip, N.Y. . . . distributed by Generix Drug Corp., Hollywood, Fla.") was a new drug without an effective approved New Drug Application—505(a).

DISPOSITION: The article was claimed by the shipper. Pursuant to stipulation of the parties, the action was ordered transferred to the Eastern District of New York for possible consolidation and trial with a similar action. Ultimately, a consent decree of condemnation ordered the article destroyed. (F.D.C. No. 63073; S. No. 80-245-064; S.J. No. 7)

PRODUCT: **Furosemide tablets**, at Washington, Dist. Columbia; Civil Nos. 80-2734 and (on removal) CV-81-0964.

CHARGED 10-24-80: When shipped by Superpharm Corp., Central Islip, N.Y., 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 and demanded trial by jury. Pursuant to stipulation of the parties, the action was ordered transferred to the Eastern District of New York for possible consolidation and trial with a similar action. Ultimately, a consent decree of condemnation ordered the article destroyed. (F.D.C. No. 63209; S. No. 80-240-041; S.J. No. 8)

PRODUCT: **Homatropine methylbromide & pentobarbital combination suppositories (two different strengths)**, at Houston, S. Dist. Texas; Civil No. H-80-2008.

CHARGED 9-5-80: When shipped by G&W Laboratories, Inc., South Plainfield, N.J., the articles (labeled "Matropinal Inserts [or 'Matropinal Forte Inserts'] . . .

Comatic Laboratories, Inc., Houston, Texas") were new drugs without effective approved New Drug Applications—505(a); and, while held for sale, the articles' labeling lacked adequate directions for use and the articles were not exempt due to their new drug status—502(f)(1).

DISPOSITION: The government and the Texas distributor, Comatic Laboratories, Inc., had been involved in extensive negotiations concerning the same drug and three similar seizure actions; and there was an agreement that the government would not file for a default judgment until the distributor's attorney had contacted the firm regarding filing a claim. In the interim, the court (unaware of such negotiations) dismissed the complaint. The government moved for and was granted the reinstatement of the complaint. Ultimately, a default decree ordered the articles destroyed. (F.D.C. No. 63108; S. Nos. 80-261-522/3; S.J. No. 9)

PRODUCT: **Pentylentetrazol capsules**, and **pentylentetrazol elixir**, at Memphis, W. Dist. Tenn.; Civil No. 82-2593-W.

CHARGED 8-12-82: When the capsules were shipped by Vale Chemical Co., Inc., Allentown, Pa., and the elixir was shipped by Pharmaceutical Assoc., Inc., Greenville, S.C., the articles (labeled in part "Nicozol Each Capsule [or 'Each 5 cc.'] contains: Pentylentetrazol . . . Manufactured for Hyrex Pharmaceuticals, Memphis, Tenn.") were new drugs without effective approved New Drug Applications—505(a).

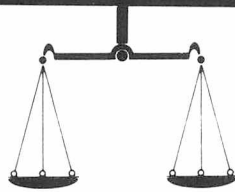
DISPOSITION: Default—ordered destruction. (F.D.C. No. 63765; S. No. 82-276-721; S.J. No. 10)

Medical Devices

PRODUCT: **Fire blanket, Water-Jel, in sealed plastic canisters**, at Lafayette, W. Dist. La.; Civil No. 82-2180, Section S.

CHARGED 9-2-82: The article (labeled in part "Water-Jel Fire Blanket For use on burn victims . . . Trilling Resources, Ltd., Hartsdale, N.Y. . . . Manufactured by Trilling Resources, Ltd., Woonsocket, R.I.") was packaged in defective, leaking containers; the article's purity and quality fell below its purported purity and quality—501(c); and the article's labeling was false and misleading in representing and suggesting that an approval of a Medical Device Application was in effect and that the device was aseptically packed and sterile—502(a).

DISPOSITION: A default decree condemned the article. Meanwhile, Steven Killingsworth, t/a Fire Stop, Inc., Lafayette, La., as owner of the articles, moved to preserve a representative number of the articles as evidence, since he was involved in a suit titled *Fire Stop, Inc. v. Trilling Resources, Ltd.*, in which the condition of the article's canisters was a material factor. The court granted the request to preserve 10 large and 10 small canisters during the



pendency of such litigation. The remaining blankets were donated to the local sheriff's department (upon the condition that they be washed) for use as bed blankets. (F.D.C. No. 63791; S. No. 82-221-702; S.J. No. 11)

CRIMINAL ACTIONS

DEFENDANT: **Harvey M. Levin, M.D.**, clinical investigator, Philadelphia, E. Dist. Pa.; Cr. No. 81-00203-1. **CHARGED** 7-9-81 by grand jury: (initial count—mail fraud) That, in accordance with the law, five specified sponsoring pharmaceutical companies had filed required IND notices with FDA so their clinical investigators could conduct drug safety and efficacy studies and such sponsoring companies were required to submit study protocols and to provide information about the progress of the new drug investigations; that the defendant (who was a clinical investigator and who, with other Philadelphia M.D.s maintained a private medical practice, known as Obstetricians & Gynecologists, Ltd.) was required to prepare and sign a Statement of Investigation form (FD-1572) before conducting human investigational drug studies, and was required to prepare case histories, to record pertinent data, to obtain the informed consent of his participating patients, and to secure the review and approval of an independent institutional review committee; that the defendant was required to complete and sign a Case Report form for each qualifying and participating patient; that the defendant had been engaged as an investigator on a fee-per-patient basis for various investigational new drug studies and had signed a Statement of Investigation form for each study he allegedly performed; and that the defendant had devised a scheme to defraud, as follows:

The defendant represented that he had successfully carried on and completed a number of investigational drug studies on proposed new drugs for relief of *postpartum* episiotomy pain when the studies had not been completed as represented, attempted to conceal the fraudulent nature of the investigational drug studies, and attempted to conceal such studies from Obstetricians & Gynecologists, Ltd., and other physicians, by converting the funds (which he received as payment) to his personal use.

In furtherance of the above scheme to defraud and obtain money, the defendant made a number of false representations: (a) created false Case Report forms purporting to reflect results of the use of zomepirac and other drugs on human subjects, (b) provided false Case Report forms to firms who compiled test results—based on such forms—for submission to FDA, (c) caused certain Case Reports to reflect certain false patient information (in order to deceive FDA and others into believing that the drug studies were based on actual clinical observations of maternity patients), (d) signed, as a witness, numerous false Patient Informed Consent forms, (e) prepared false committee minutes of a hospital clinical investigation committee, (f) concealed the

receipt of payment for the studies from Obstetricians & Gynecologists, Ltd., and others, (g) received in excess of \$140,000 for drug studies; and that, under the above circumstances, the defendant, for the purpose of executing the scheme to defraud, caused to be placed in the U.S. mails a letter addressed to Obstetricians & Gynecologists, Ltd., Cherry Hill, N.J.—18 U.S.C. 1341; and (subsequent count) that, under the above circumstances, the defendant, knowingly and willfully, in a material matter within FDA jurisdiction, submitted to a sponsoring pharmaceutical company certain Case Report forms containing the alleged results of a study concerning zomepirac on humans and representing that the defendant had completed the study and had developed data with respect to human reactions to zomepirac, when the investigation, in fact, had not been completed and the Case Report forms were false—18 U.S.C. 1001.

DISPOSITION: The defendant offered a plea of *nolo contendere*. However, the court refused to accept such plea. Subsequently, the defendant pleaded guilty. He was sentenced to one year and one day imprisonment, to be followed by a five-year period of probation. (Misc. No. 730; S.J. No. 12)

CIVIL CONTEMPT ACTIONS

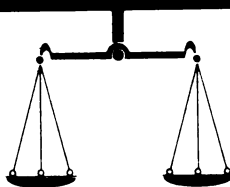
DEFENDANTS: **Miami Serpentarium Laboratories, Inc.**, **William E. Haast**, president, and **Nancy G. Harrell**, vice president; and their exclusive distributor, **Miami Venom Institute, Inc.**, and **Frederick Sessler**, institute president, and **Lloyd Feanny, M.D.**, former institute medical director; Miami, S. Dist. Fla.; Civil No. 80-2735-CIV-JE.

CHARGED 10-5-81 in a motion for a show cause order for civil contempt: That, with actual notice of the court's order of preliminary injunction (see S.J. No. 14 of this issue of *FDA Consumer*), the defendants, in violation of the court's order, continued to manufacture, promote, label and distribute PROven, in much the same fashion as before the preliminary injunction.

DISPOSITION: The court found on March 30, 1982, that the defendants in the civil contempt action were in contempt for the violations. However, under the circumstances of the case, the court imposed no sanctions at that time. Nevertheless, the court advised the parties "that if future violations occur, the court will consider both past violations and future violations in determining what sanctions to impose for any future violations." (Inj. No. 971; S. No. 81-270-961 et al.; S.J. No. 13)

INJUNCTION ACTIONS

DEFENDANTS: **Miami Serpentarium Laboratories, Inc.**, **William E. Haast**, president, and **Nancy G. Harrell**, vice president; and their exclusive distributor, **Miami Venom Institute, Inc.**, and **Frederick Sessler**, institute president, and



Lloyd Feanny, M.D., former institute medical director; Miami, S. Dist. Fla.; Civil No. 80-2735-CIV-JE.

CHARGED 10-3-80 in a complaint for injunction and amended 10-7-80 and 12-17-81: That the defendants, at their Miami plant, manufactured, processed, packed, labeled, held and distributed in interstate commerce a biological drug product called PROven, which contained interstate components; that the labeling of PROven lacked adequate directions for use; that the label of PROven stated "Caution New Drug—Limited by Federal Law to Investigational Use," which falsely suggested that PROven had a valid investigational new drug exemption (IND), when in fact PROven was not the subject of an approved IND; that PROven was fabricated from two or more active ingredients and its label lacked the established name and quantity of each active ingredient; that the circumstances used for the manufacture, processing, packing and holding of PROven at the defendants' plant failed to conform with current good manufacturing practice; that PROven was not manufactured and prepared at a licensed establishment; that FDA inspections revealed a number of specified deviations from current good manufacturing practice; and that the defendants were well aware that their activities were not within the law—502(f)(1), 502(a), 502(e)(1)(A)(ii), 501(a)(2)(B), 42 U.S.C. 262(a), 42 U.S.C. 262(b).

DISPOSITION: The defendants denied that PROven was a biological product subject to 42 U.S.C. 262(a) and denied some of the charges. The government's motion for a Temporary Restraining Order and application for a preliminary injunction were consolidated for trial. Meanwhile, the defendants conceded and agreed that a preliminary injunction should be granted to the government, but requested the inclusion in the preliminary injunction of certain exceptions. The government moved for partial judgment on the pleadings, arguing that it was entitled to judgment on all charges except 502(f)(1).

The court entered an order of preliminary injunction enjoining the defendants from manufacturing, promoting and distributing PROven in violation of certain licensing and misbranding provisions of the Public Health Service Act and certain adulteration and misbranding provisions of the Food, Drug, and Cosmetic Act. However, wholly *intrastate* operations were not restrained, and the defendants were not prevented from operations under an authorized "short supply" arrangement pursuant to 21 C.F.R. 601.22.

The defendants moved for a conference to clarify certain conditions of the preliminary injunction, *i.e.*, to outline the defendants' plan for intrastate manufacturing, packaging, labeling and distribution of PROven. The government moved for the issuance of an order to show cause in civil contempt (see S.J. No. 13 of this issue of *FDA Consumer*). The government moved to amend the complaint to add the defendants' exclusive distributor and the distributor's president and its former medical director. The government also moved for summary judgment on both the motion for civil

contempt and the motion for entry of a permanent injunction.

There was a consolidated trial before the court on the motion for a permanent injunction and the motion for civil contempt. After trial before the court, the court issued a permanent injunction. On March 30, 1982, the court found that PROven was an article of drug within the meaning of 21 U.S.C. 321(g), and that it was also a toxin, and, therefore, a biological product within the meaning of the PHS Act, 42 U.S.C. 262(a). Since the defendants had not obtained the necessary PHS licenses, they violated the law by providing PROven to persons who cause the product to be carried outside of Florida.

The court also concluded that PROven was composed of interstate components; that it was immaterial whether the ingredient was characterized as "active" or "inactive" because the safety, purity, potency and effectiveness of the drug depends upon both its active and inactive ingredients; and that federal jurisdiction was not defeated because the interstate constituent composed only a minute fraction of the article. The defendants had stipulated that animal and clinical data derived from extensive, scientifically controlled testing do not exist for PROven, and the court found that, without such test data, the drug could not be labeled for any use, and *a fortiori*, lacked adequate directions for use.

In accordance with the court's findings, the court issued a permanent injunction, with respect to PROven or any similar drug, which enjoined: (a) any interstate sale of PROven or any similar article unless and until the product and its manufacturing establishment had been licensed or unless and until an Investigational Exemption had been accepted by FDA; (b) the interstate shipment ("including the delivery of any such drug to one or more intermediaries who ultimately sent or carried the article out of the state") or "promoting, manufacturing, processing, packing, labeling or holding PROven or any similar article designated by any other name after shipment of one or more of its ingredients (including active and inactive ingredients, product containers, and/or closures in interstate commerce)" unless and until a number of specified conditions were met concerning the establishment of current good manufacturing practice confirmed by an inspection and a corrective action report, by an expert. The decree of permanent injunction also ordered the delivery to FDA of "the names and addresses of each practitioner, clinic, institution or person to whom the Defendants distribute PROven or any similar article in the future," until the defendants acquired specified licenses.

Subsequently, the government moved to tax the defendants with both the litigation costs (\$1,228.70) and the investigational costs (\$6,369) that the government had incurred. The defendant opposed the government's motion. Upon consideration of the record and after oral argument, the court granted the government's motion to the extent that costs were taxed against the defendants in the amount of \$1,228.70. (Inj. No. 971; S. No. 80-193-581; S.J. No. 14)

Have fun in the sun, but know your SPF ...*

** Sun Protection Factor, suggested by a panel of experts and found on many suntan lotions and creams:*

SPF 2 to 4: For people who seldom burn but tan profusely.

SPF 4 to 6: For those who tan well with minimal burn.

SPF 6 to 8: For people who burn moderately and tan gradually.

SPF 8 to under 15: For maximum protection, with little tanning resulting.

SPF 15 and over: An "ultra" rating that permits no tanning; it's for people who never tan but always burn.

