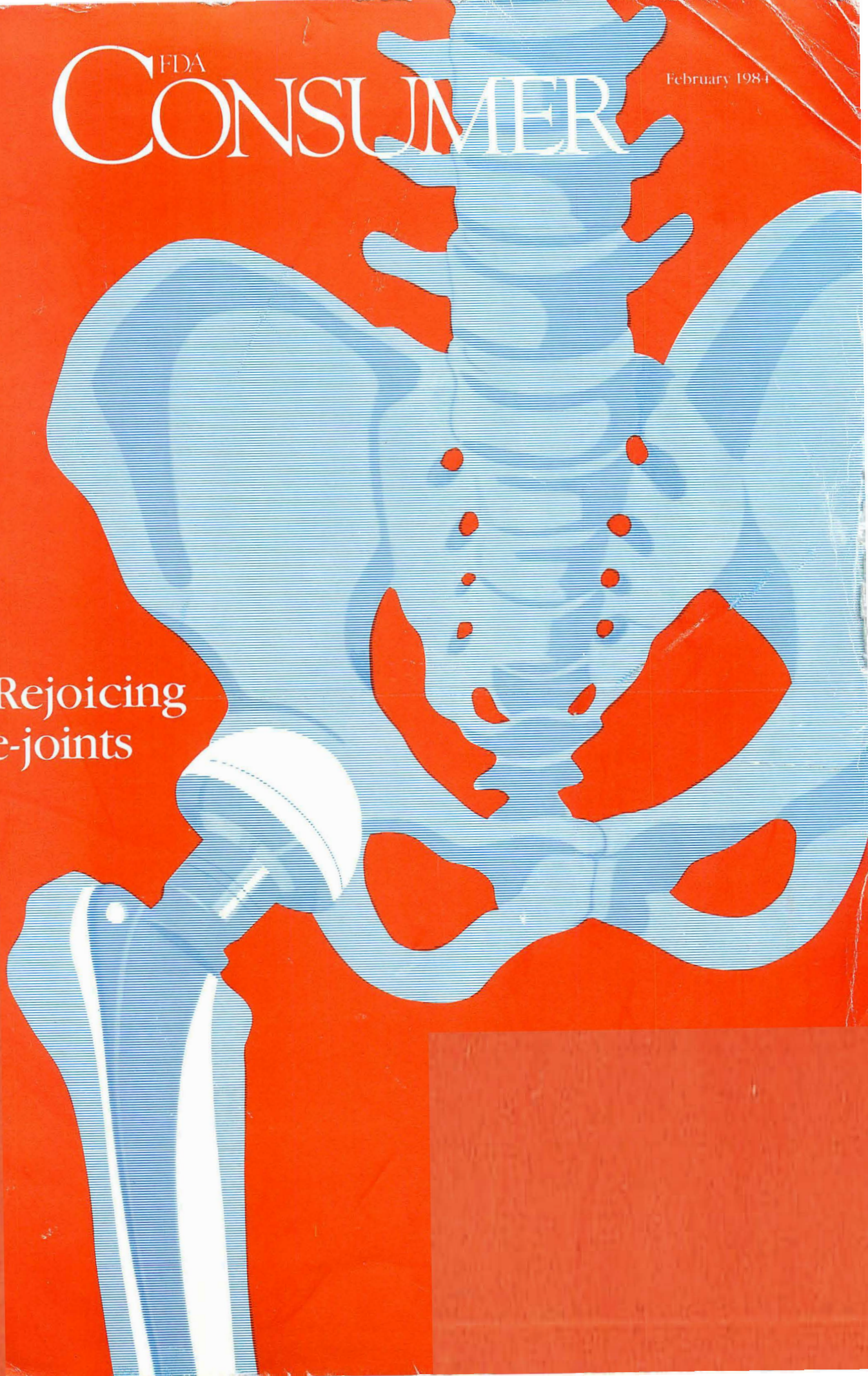


FDA CONSUMER

February 1984

There's Rejoicing
Over Re-joints





FDA CONSUMER

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The Horseshoe Crab: A True Blueblood

Scientists bleed horseshoe crabs for their blue-colored blood, which is used to detect bacteria in drugs and devices. The process leaves questions about the crab's survival.

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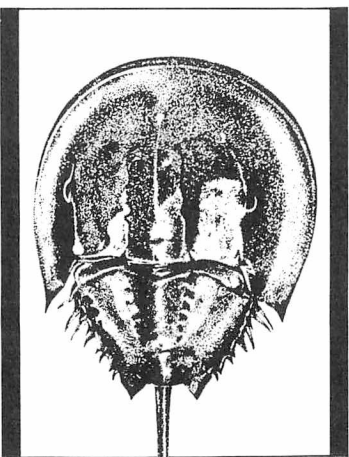
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Putting the squeeze on those who practice economic deception in food labeling is a responsibility of FDA, and orange juice processing is one field where such deception is difficult to detect. How FDA keeps abreast of economic cheating in food labeling is treated in an article, On Making Food Labels Truthful, starting on page 22.

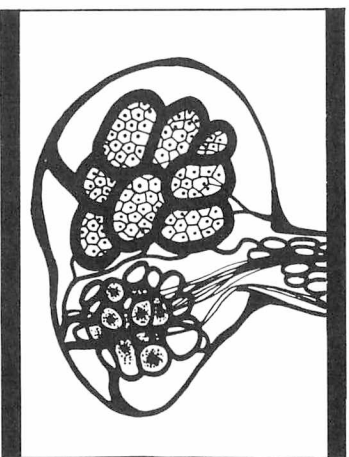
Margaret M. Heckler
Secretary, U.S. Department of
Health and Human Services

Roger W. Miller/Editor
Harold C. Hopkins/Editorial Director
Jesse R. Nichols/Art Director

Cover Design: Zeb Rogerson



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Patient Leaflets Proliferate

Providing patients with information about the drugs they take has become a popular activity, and the number of leaflets available is increasing by leaps and bounds.

The American Medical Association announced last November that it had published 20 new Patient Medication Instruction (PMI) sheets, bringing to 60 the total in its series of information sheets on therapeutic drugs. The list now includes over-the-counter as well as prescription products.

The PMI sheets were developed by AMA for physicians to give to patients at the time a drug is prescribed. Among the drugs covered by the newest PMIs are phenothiazines, tricyclic antidepressants, antihistamines, propoxyphene (Darvon), acetaminophen, aspirin, potassium supplements, and methotrexate.

PMI sheets are bound 50 to a pad and cost \$1 per pad.

The American Association of Retired Persons and National Retired Teachers Association (AARP/NRTA) Pharmacy Service now has 55 leaflets in its drug information program. The leaflets cover more than 190 drugs, representing 80 percent of the drugs that the elderly take.

Called Medication Information Leaflets for Seniors (MILS), the AARP/NRTA leaflets were the first national voluntary effort to provide written drug information to consumers at the time a prescription is filled. By the end of 1983 something in the neighborhood of 3 million leaflets had been distributed, according to the Pharmacy Service. A membership survey showed that 90 percent of those responding found the leaflets useful and 76 percent said they keep them for future reference.

A new program, launched in September 1983 by the National Association of Retail Drugists (NARD), involves Patient Information Leaflets (PILs) abstracted from the *United States Pharmacopeial Dispensing Information* and its Updates. The 32 leaflets, to be provided by pharmacists when prescriptions are filled, cover 200 drug entities, about 80 percent of the drugs

dispensed in a community pharmacy.

The PIL sheet can be personalized for the individual patient. Type size is large and easily readable by patients, particularly the elderly. And, the association points out in the September 1983 issue of the *NARD Journal*, "the word 'pharmacist' appears five times in the text, attesting to the pharmacist's expertise."

The leaflets cover single entities, such as furosemide, cimetidine, allopurinol and nitroglycerin, and families of drugs, including beta-adrenergic blockers, cephalosporins, phenothiazines and thyroids. Although the program is relatively new, some 600,000 PILs had been distributed to pharmacists by the end of November 1983. Originally intended for NARD members only, the leaflets are now available to other pharmacists.

Cough Syrups May Switch

FDA has proposed switching two prescription cough-suppressant drugs to nonprescription status and sale. The drugs—benzonatate and chlorphedianol—have been used safely for more than 20 years.

The change is part of a proposed standard for over-the-counter (OTC) antitussives—cough-relief products—published in the Oct. 19, 1983, *Federal Register*. FDA issued the proposed standard after reviewing the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasmatic Drug Products. The panel was one of 17 non-government advisory groups assisting the agency in a massive review of the safety and effectiveness of ingredients in all OTC drugs.

Because the two prescription drug ingredients were not reviewed by the panel, FDA will not permit their OTC marketing until public comments on the proposed standard have been evaluated and the standard has become final.

FDA concurred with the panel that five ingredients already in nonprescription cough-cold products are safe and effective. These are dextromethorphan and dextromethorphan

hydrobromide and codeine, codeine phosphate and codeine sulfate. (In many states codeine is a prescription drug.) Codeine-containing products should have directions clearly stating that a doctor should be consulted before giving the preparation to a child under the age of 6, according to FDA's proposed standard.

The agency also said that new data proved camphor and menthol are safe and effective cough-relieving drugs. Previously, the panel said there was not enough evidence to show these ingredients were effective. Camphor and menthol are used in ointments rubbed on the chest, and menthol is also used in throat lozenges.

FDA made a number of changes in the labeling for cough-relief products. One of them is to allow the product to be called a "cough suppressant" or "antitussive (cough suppressant)" instead of just an "antitussive." Manufacturers may also include in labeling a statement that indicates an antitussive can alleviate, decrease or suppress a cough "to help you get to sleep."

The original panel report was published in September 1976 (see "The Common Cold: Relief But No Cure" in the September 1976 issue of *FDA Consumer*). FDA is issuing the proposed standards based on this report in segments. The antitussive drug standard is the third to be published. Previously issued were proposed standards for anticholinergic, expectorant and bronchodilator drug products (see "Drug Standards Offered" in the Updates section of *FDA Consumer*, October 1982, and "Help for Wheezers" in Updates, *FDA Consumer*, February 1983. "The Common Cold: Relief But No Cure" is still available as a reprint. Copies may be obtained by writing to FDA, HFE-88, 5600 Fishers Lane, Rockville, Md. 20857).

Starch Blockers On Losing Strike

Ruling for FDA and against the General Nutrition Corp. and nine other promoters of starch blockers, a federal judge in New York concluded that "starchblocker pills are declared drugs under the [Food, Drug, and Cosmetic] Act. Their seizure

is therefore permissible."

The other plaintiffs in the case were American Health Products Co. Inc., General Nutrition Center Inc., Melva Natural Products Inc., Nature's Bounty Inc., Nutrition Headquarters Inc., Phoenix Laboratories Inc., R-Kane Products Inc., and Sunrise Chemical Inc.

The ruling by U.S. District Judge Abraham D. Sofaer of the Southern District of New York was the third federal court opinion that has held starch blockers to be unapproved new drugs. The New York court's opinion can be appealed within 60 days.

Starch blocker tablets were the dietary fad of a year or so ago. Their manufacturers claimed that they prevented, or "blocked," the absorption of starch by the body. This, they said, would allow a person to eat whatever starchy foods are desired without weight gain.

FDA maintained that since starch blockers are claimed to alter a normal function of the body they should be regulated as drugs, not foods. No investigational new drug (IND) application or New Drug Application (NDA) has been filed with FDA for any starch blocker. (An IND is an application to do clinical testing of a new drug, and an NDA is an application for approval of a new drug.) Three independent clinical trials have concluded that starch blockers don't work.

Between September 1982 and mid-November 1983, FDA seized starch blockers worth more than \$3.5 million retail.

One seizure took place this past summer, when the Connecticut Department of Consumer Protection reported starch blockers being sold in various parts of the state. An FDA investigator from the East Hartford resident post visited General Nutrition Corp. stores in Waterbury, Milford, Trumbull, Bridgeport, Stamford and Farmington.

At the six locations of this national health food chain, the investigator found a total of 1,662 bottles (30 tablets each) and 271 bottles (100 tablets each). He also found a small surprise: 115 shakers of a powdered concentrate labeled "Starch Blocker Sprinkles," a new form of the illegal product. The label on the shakers said that using the sprinkles

on food would "put a little fun back in your diet."

The fun aspect of starch blockers was lost on the investigator. He returned to the GNC locations with a U.S. marshal, who seized the several stocks of tablets and sprinkles, valued at \$25,000, for burial in a landfill.

Canada, Britain, Australia, Israel and West Germany also have taken regulatory action against starch blockers.

In a separate action, on Oct. 31, a U.S. Postal Service administrative law judge found that General Nutrition Corp. of Pittsburgh was engaged in conducting "a scheme for obtaining money through the mails by means of false representations regarding the product Starch Block. . . ." Specifically, the product ads were found to be false because starch blockers are ineffective for preventing the digestion of starch. GNC's attorney has said the ruling will be appealed.

Drug Combinations Curbed

To curb abuse of over-the-counter drug products being sold as if they were controlled substances or "look-alike" drugs, FDA has declared that the following products will no longer be allowed on the market:

- OTC products labeled as stimulants that contain anything other than caffeine as the active ingredient
- OTC products labeled for any purpose when they contain as their only active ingredients combinations of caffeine and ephedrine (or pseudoephedrine), caffeine and phenylpropanolamine (PPA), or phenylpropanolamine and ephedrine (or pseudoephedrine).

FDA's decision, in the form of an advisory opinion, was published in the Nov. 18, 1983, *Federal Register*. In addition, the agency mailed letters to more than 350 firms identified as manufacturers/distributors of these products advising that, with one exception, all of these products would be subject to regulatory action immediately if not removed from the market.

The only exception: products that contain caf-

feine and phenylpropanolamine as their sole active ingredients that are labeled only as appetite suppressants, diet aids, or diet aids/stimulants, and are manufactured or in the process of manufacture before the November date. These products have a significant history of use for purposes other than "recreational use" and the agency thus will allow manufacturers to use up existing stocks.

(For more information on such look-alike drugs, see "On The Trail Of Counterfeit Drugs" in the December 1981-January 1982 *FDA Consumer*.)

Reprints Available

Reprints are available of the articles "Herbs Are Often More Toxic Than Magical" and "Using Drugs To Lift That Dark Veil Of Depression," both from the October 1983 issue of *FDA Consumer*, and of "Water: The Number One Nutrient" from the November 1983 issue.

In addition, "How To Talk To (And Listen To) Your Pharmacist," from the April 1980 *FDA Consumer*, has been updated and reissued as a reprint. 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.

Quaaludes Discontinued

Lemmon Co. of Sellersville, Pa., the only legal manufacturer of methaqualone (or Quaalude) in the United States, halted manufacture of the drug and stopped distribution Jan. 31. While maintaining that the sedative-hypnotic is safe and effective, the company acknowledged that it had become widely abused, particularly by so-called "stress clinics."

Lemmon said it abandoned manufacture of the drug after discussions with FDA and the Drug Enforcement Administration.

Methaqualone is abused as a "downer" and can

be fatal when mixed with alcohol. Because of this potential for abuse, in 1973 the drug was placed in Schedule II of the Controlled Substances Act, the most restricted category for drugs with an accepted medical use. FDA has steadily reduced its recommendation to DEA for the manufacturing quota of the drug, which is based on its anticipated legitimate use. Prescriptions declined from more than 4 million in 1973 to less than 300,000 in 1982, a reduction of more than 90 percent, including those written in "stress clinics."

FDA told a congressional subcommittee last October that its recommended manufacturing quota might well be reduced further in coming months. Legislation subsequently reported by the House Committee on Energy and Commerce would have outlawed methaqualone.

States Save On Drugs

Twenty-four states and the District of Columbia saved millions of dollars on drugs in 1983 by using computerized data from FDA about the track records of prospective drug suppliers.

The information helped the states buy drugs for their hospitals and clinics at lower prices by identifying those low bidders who are reliable suppliers of quality products.

In this quality assurance program, which began with a pilot study involving five states in 1981, FDA provides a monthly list of acceptable sources for approximately 3,500 drug products. The information comes from inspections of drug manufacturers, laboratory tests, compliance records, and drug marketing applications. Similar data have been provided to the Defense Department and other federal purchasers of drugs since 1965.

FDA also provides state personnel with training on videotape about how to interpret the data, saving the cost of travel to FDA headquarters.

- State users say the program:
- increases competition for the large quantities of drugs they purchase
 - provides objective data for contracting decisions involving multiple bidders
 - gives reliable information about a low bidder's

acceptability

New York state alone reports savings from the program in excess of 1 million dollars a year.

States participating in the program are Arizona, Arkansas, California, Delaware, Florida, Georgia, Louisiana, Maryland, Michigan, Minnesota, Mississippi, Missouri, New Jersey, New York, Oregon, Pennsylvania, Rhode Island, Tennessee, Texas, Virginia, Washington, West Virginia, Wisconsin, Wyoming, and the District of Columbia. In addition, the Canadian government's Health Protection Branch receives the FDA data.

Because the quality assurance information is already computerized and can be printed and distributed at virtually no cost, there is no charge to states that receive it. All states are eligible to participate in the program.

Advice On Tampons

Women will soon receive advice on the outside of all tampon packages urging them to use the least absorbent tampon that meets their needs.

Since 1982, FDA has required that this advice be part of the information on toxic shock syndrome (TSS) provided to tampon users, but it generally has been included inside the box as part of a package insert. Although tampon use in general has been associated with TSS, one study has also suggested that the risk of getting TSS is even greater with higher absorbency tampons.

Because of concern that manufacturers' promotion of their products as providing greater protection and high absorbency could obscure the advice suggesting use of the least absorbent tampon possible, the National Center for Devices and Radiological Health wrote to all manufacturers in June 1983 recommending that the advisory message be put on the outside of the package.

Manufacturers were asked to inform the center of any plans to adopt the additional labeling. By the end of August all had agreed to adopt the outside labeling, and two stated they had already done so before receiving the center's request.





The Horseshoe Crab: A True Blueblood

by David R. Zimmerman

Boys from a nearby summer camp race along the beach and into the shallow waters of St. Joseph Bay, on Florida's Gulf Coast. Under the direction of marine biologist Anne Rudloe, Ph.D., of Florida State University, they are hunting scientific treasure: 10,000 numerically coded yellow plastic markers.

Each tag is attached to the tough, brown, horny shell of one of the bay's resident horseshoe crabs. Several months earlier two dozen amateur scientists from the nonprofit Earthwatch organization caught and tagged the animals, using electric hand drills to make anchor holes. Blood was extracted from about half of the animals and noted on the appropriate tags. Then all the animals were turned loose into the water again. The young campers now are trying to recapture them for a reward of \$1 per tag.

The aim of Dr. Rudloe's tag game: to find out if the recent heavy exploitation of these ancient armored creatures is a threat to their survival. What concerns her is the rush of biomedical scientists and drug manufacturers to use the horseshoe crab to make life-saving human drug products.

The blood of the horseshoe crab was found, in the 1960s, to be highly valuable because it reacts with, and so can be used to detect, bacterial endotoxin, a dangerous poison produced by some infectious bacteria that can bring on fever, pain, inflammation, shock—and sometimes death.

A substance in this blood also reacts with the red and white cells in human blood, particularly the cancerous white cells of some leukemia patients. One day it may be used for diagnosing this illness.

In their forays into the surf, the collectors capture horseshoe crabs measuring almost a foot across the thick frontal helmet, through which the animal peers out at its world with seven eyes, set in four concealed peekholes. Mature crabs—some as old as the collectors—crawl ashore on summer high tides to deposit their eggs in the sand. They spend most of their lives in the nearby shallows, going deeper in winter. Oddly, all four horse-

shoe crab species inhabit only the eastern edges of the continental land masses of North America and Asia. The single North American species, *Limulus polyphemus*, is found from Maine to Yucatan.

The horseshoe crab is not a crab at all, but belongs to the spider class, Arachnida. It appears to be most closely related to scorpions—though its tail is stingless—and to ancient trilobites, whose form it recapitulates in the larval stage.

Horseshoe crabs originated some 400 million years ago. "It's an animal that's been made to stay around," says Elias Cohen, Ph.D., an immunologist at the Roswell Park Memorial Institute in Buffalo, N.Y. Cohen has been a leader in biomedical research involving the animal and in efforts to protect this unusual creature.

The horseshoe crab may fare better than the owl monkey, the rhesus monkey and the chimpanzee, which have become subjects of conflict between the laboratory scientists who use them and environmental scientists who study them in the wild and try to protect them. Many horseshoe crab users, like Cohen, also are interested in conserving the species. Dr. Rudloe's study is funded by FDA, which regulates medical products made with the animal's blood. She has been encouraged by drug companies, who hope to produce horseshoe crab blood products on a continuing basis.

To obtain the blood, commercial collectors place the animal on a rack, push a hypodermic needle into the horseshoe crab's heart, attach a tube, then collect the blood that drains slowly out by gravity in a sterile container. The blood has a striking royal blue hue because its oxygen-carrying molecule, hemocyanin, contains copper instead of iron (which gives red blood its color). Depending on the animal's size, it will give up one to seven ounces of blood in this way. The collectors and their drug company buyers are reluctant to discuss the prices paid for the blood.

"You're dealing with big money," one scientist says. "There are people who've made hundreds of thousands of dollars with the blood of this animal."



But to Dr. Rudloe, the more basic question is: How harmful to the horseshoe crab is this bloodletting?

"They don't seem to react too badly," she says.

"When we take them out of the racks, they move about fairly vigorously." FDA, she says, requires that bled crabs be returned to salt water within 72 hours and, as far as anyone knows, most survive their blood loss. But no one knows for sure, and Rudloe's study is the first attempt to assess their recovery—or lack of it—in a scientific way.

She and her Earthwatch assistants bled 5,000, or about half, of the crabs they caught. Some 60 gallons of the blood was donated to Dr. Cohen and other researchers. The other 5,000 crabs were not bled. Now, with the help of boys from Camp Nautilus, and fishermen, shrimpers, and others on the bay, Rudloe is retrieving all the tags she can, to see if she will get fewer back from bled horseshoe crabs than from the unbled ones.

Over two summers the collectors retrieved 1,582 of the 10,062 tags, or roughly one tag in every six. The return rate was about 10 percent lower for the crabs that had been bled than for the unbled control animals, which indicates that bleeding does kill some crabs.

The difference is "just barely" significant statistically, Dr. Rudloe says, adding, "not really enough to warrant anything drastic in the way of changing the harvest procedures." Rudloe says she bases this conclusion on comparisons with other commercial fisheries, in which a short-term 10 percent reduction in population due to fishing does not seriously threaten the population's existence.

The gravity bleeding method thus may cause little harm. But Rudloe has heard rumors that some collectors are trying to obtain more blood by bleeding the animals with vacuum pumps—which could be lethal. Worse, a biomedical researcher in New England suspects that truckloads of horseshoe crabs are being carried inland for bleeding. He thinks it unlikely that they are returned to the sea.

"They are being shipped by the thousands to companies that are using them," says blood specialist Jack Levin. Levin is a doctor at Johns Hopkins University in Baltimore who studies horseshoe crabs each summer at the Marine Biological Laboratory in Woods Hole, Mass. He says that the laboratory's collectors once could find 500 large animals in a day along one Cape Cod beach. Today they are lucky to find 50. He blames blood collectors. But around Florida, Rudloe says, no serious population declines have been documented, or even observed, although there are reports of local declines in Mobile Bay, and other places, declines that predate the drug companies' interest in these animals.

Outside the biomedical realm, horseshoe crabs have few human uses. Most people shun them as food, although the Thais eat their eggs. American Indians once

used the sharp tails for spearheads; eel fishermen now crush them to bait their traps; shell fishermen destroy them as a competitive threat. But Dr. Levin reckons these are minor depredations when compared to bloodletting for science and medicine.

Although information is sparse, Rudloe cites a recent drug industry estimate that 30,000 horseshoe crabs are bled each year along the Eastern Seaboard. This could be a tiny number, among uncounted millions. But the collectors certainly reach for the larger animals, which are the breeders. Since it's possible that horseshoe crabs don't begin reproducing until they are 5 to 10 years old—scientists simply don't know for sure—the loss of a relatively few mature ones could compromise the population as a whole.

Industrially polluted water appears to kill horseshoe crabs. But the very traits that make the animal medically valuable also protect it against most pollutants, and it continues to thrive in sewage-laden harbors of both the United States and Japan. In fact, the species' internal system of defense against invading bacteria is impressive.

The species needs strong antibacterial defenses, Rudloe believes, because the shallow bay waters it frequents contain much decaying matter and bacterial scum. Yet, horseshoe crabs lack an immune system, the multi-targeting defense method that allows modern animals to produce antibodies directed at specific bacterial species and many—perhaps millions—of other menacing alien molecules. By contrast, the horseshoe crab's primitive but extremely potent defense system, like a cannon fixed in concrete, seeks out a handful of key biochemical molecules that are constituents of most bacteria that may infect them.

It is this remarkable self-protective method that has so captivated biomedical scientists. Here is how the self-protection system works:

The principal protector of the horseshoe crab's internal environment is a primitive white blood cell called the amebocyte. Like the free-living amebas for which it is named, it appears self-directed as it perambulates the bloodstream in search of endotoxin-producing bacterial invaders, including coliforms and other fecal bacteria. When it finds such a bacterium, the amebocyte releases an enzyme and a clotting substance, which reacts to transform the liquid blood around the bacterium into a sticky gel. The bacterium is immobilized and dies, like a tiger in a tar pit. Usually only a tiny bit of gel is formed, but in a massive bacterial infection, much of a horseshoe crab's blood turns to jelly—and the animal may die as a result.

The active ingredients in this response can be extracted from the amebocytes; the purified extract is called LAL, for limulus amebocyte lysate. LAL is incredibly sensitive: It will detect as little as a billionth of a gram of endotoxin in an eyedropper of water.

The present test for endotoxin requires injecting the

drug product into three to eight rabbits, then monitoring them carefully for several hours to see if they become feverish. This is expensive and slow, and takes many rabbits' lives. Blood specialist Levin decided that the same information might be obtained more expeditiously using horseshoe crab blood. Dr. Levin and his colleague, Dr. Frederick Bang, demonstrated that the crab's blood could detect endotoxin.

Producers of LAL test kits freeze-dry the lysate extract. It is then reconstituted with sterile water and added to a sample of the drug or antibiotic or biological product to be tested or, in the case of a medical device, to the saline solution in which the device has been washed. If endotoxin is present in the sample, a firm clot will form. In this way manufacturers can withhold from distribution products contaminated with endotoxin levels that could cause serious reactions.

"The test is now generally accepted as the best *in vitro* [test tube] assay for endotoxin," hematologist Peter A. Tomasulo, M.D., of the Milwaukee Blood Center, told a Woods Hole conference on horseshoe crabs and medicine several years ago. "The test is simple and easy to learn, and requires no sophisticated equipment."

The test's principal users thus far are drug companies, for whom, Levin says, it provides a far more sensitive endotoxin assay than the rabbits.

The LAL test also is being used to detect endotoxin in the body fluid specimens withdrawn from critically ill patients, although FDA has not specifically approved it for this purpose. It is particularly valuable, Levin reports, in the diagnosis of bacterial meningitis, a dangerous infection of the brain's membranes.

"Of all the infectious diseases we treat," Levin says, "meningitis is the one in which rapid diagnosis and treatment are particularly critical. The difference between treating now and in six hours may be life and death."

The standard tests are complicated and time-consuming. Using the experimental LAL test and a single drop of spinal fluid from the patient, meningitis due to gram-negative bacteria can be diagnosed in an hour, speeding the start of appropriate antimicrobial therapy.

Development of LAL testing of blood has been slower, Dr. Levin says, because blood produces chemicals that mask the endotoxin's presence. Effective means need to be developed to remove them. The test has a good potential for detecting bacteria in urine.

Meanwhile, Dr. Rudloe worries about the horseshoe population. "A horseshoe crab," says the marine biologist, "has needed little else than a sandy beach, a sandy and somewhat estuarine tide flat next to it, and sand bottoms offshore. Our current interest in it as a biomedical resource must not endanger this elegantly adapted species and bring its long story to an end."

David R. Zimmerman is a freelance writer.

The Pituitary: A Kernel Of Wonder

by Tim Larkin

The pituitary is truly one of nature's wonders. Consider this pea-sized object, nestling in a saddle-shaped bed of bone and hanging by a slender stalk from the underside of the brain. This object, weighing one-fiftieth of an ounce, is somehow capable of producing chemical compounds that in complexity and efficiency make the products of modern industrial plants seem like Stone Age technology. This wonder within, the pituitary gland, may well be the most concentrated chemical factory in existence.

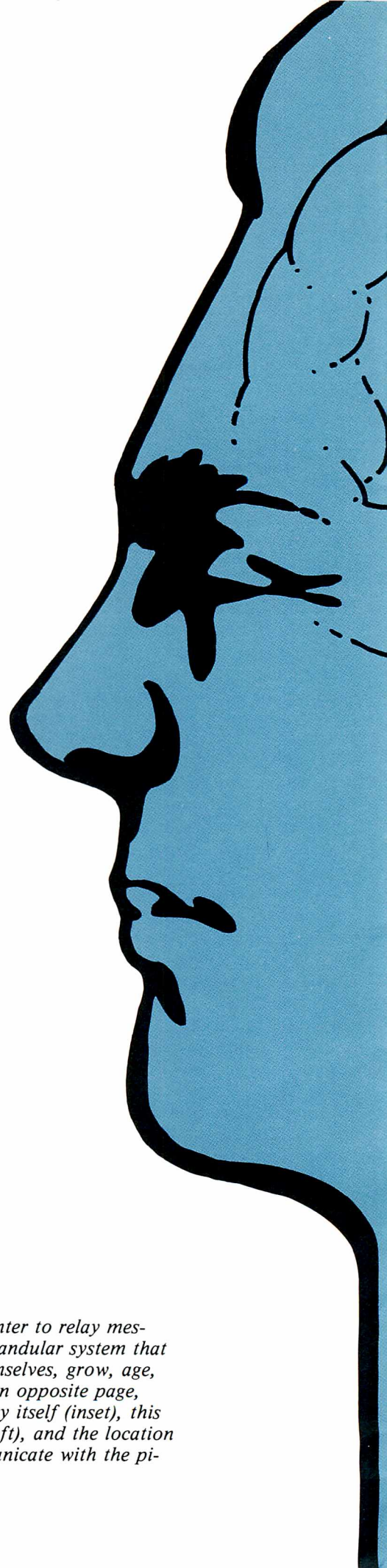
Once thought to be no more than a source of mucus (in 1543, the great human anatomist Andreas Vesalius gave the gland the Latin name *pituita*, source of our word "spit"), the pituitary is the body's master gland. As such, it acts like a control center for the finely tuned, interconnected glandular system (the endocrine system) responsible for processes of birth, growth, aging and for the smooth everyday functioning of the body. Unless the pituitary properly receives messages (such as "releasing factors") from the hypothalamus section of the brain, and unless it then sends out precisely metered medical signals at the proper time, and unless it in turn properly receives signals fed back to it from other glands, life swiftly becomes discordant, leading to bizarre disorders or to death. No matter how the brain, heart, liver, kidneys, and all other organs might operate, no matter how well we might be endowed genetically, a faulty pituitary can make life nasty, brutish and short.

The signals emitted and received by this master gland are of a special kind called "hormones" (from a Greek word meaning to excite or stir up). Hormones are actually molecules secreted by one cell type that travel through biological fluids to convey a message or regulatory signal to another cell type.

As the pituitary's hormones are released into the bloodstream, they have contact with every area of the body, but only the target organ or function is programmed to receive and react to the message carried by a particular hormone.

Based on current knowledge, the human pituitary manages to achieve all its vital, complex work by secreting each day just one-millionth of a gram of eight different hormones—two from the rear, or posterior, section, and six from the front, or anterior, section. Since the output of this master gland is so small, research on the chemical structure of pituitary hormones has been extraordinarily difficult. For example, to get one milligram of pure thyrotropin-releasing factor (TRF), scientists at the Tulane University School of

The pituitary gland acts as a control center to relay messages from and to the interconnected glandular system that determines how humans reproduce themselves, grow, age, and carry on the other life processes. On opposite page, drawings show likenesses of the pituitary itself (inset), this gland and its setting in the brain (top left), and the location in the body of other glands that communicate with the pituitary, using hormones as signals.



1. Hypothalamus
2. Pituitary Stalk
3. Pituitary
4. Kidney
5. Thyroid
6. Testes (Ovaries in women)
7. Statural Growth
8. Breast (women)



Medicine had to make extracts from some 2 million pig brains and collect, dissect and process 5 million fragments of sheep hypothalamus—involving 500 tons of brain tissue.

The pituitary's posterior section is responsible for releasing vasopressin, or antidiuretic hormone (ADH in the hormone "alphabet"), and oxytocin, both stored in the pituitary after being created in the hypothalamus, from which the pituitary is suspended. ADH is released when the body is under stress, and signals the kidneys to absorb water to maintain the correct concentrations of minerals in blood and body fluids. Should the pituitary produce insufficient ADH, a condition called diabetes insipidus occurs (this is not the same as diabetes mellitus, also called "sugar diabetes"). Those suffering from this disorder produce large amounts of dilute urine—as much as four gallons a day—a loss which creates an unquenchable thirst. A synthetic form of ADH is one of the treatments for diabetes insipidus. The other posterior hormone, oxytocin, is believed to help regulate the force of uterine contractions during birth and subsequent milk production in response to the suckling action of the newborn infant.

The pituitary's six anterior hormones include thyroid-stimulating hormone, TSH; adrenocorticotrophic hormone, ACTH; human growth hormone, HGH (also known as the somatotrophic hormone); follicle-stimulating hormone, FSH; luteinizing (ovum-releasing) hormone, LH; and prolactin, PRL, which induces milk production.

The feedback mechanism central to the proper functioning of the pituitary and its target glands is clearly seen in the way TSH works. When TSH reaches the thyroid, that gland begins to produce its own hormones. When the pituitary in turn detects an increased concentration of these thyroid hormones in the blood, it reduces its output of TSH. Responding to this lower TSH concentration, the thyroid then also slows down its production of hormones. This decreased level of thyroid hormones is detected by the pituitary, which then increases TSH production. Thus, the pituitary also works like a kind of chemical thermostat, maintaining hormonal balance by receiving signals and re-

acting to them.

The importance of a pituitary that clearly perceives and properly reacts to these signals can be seen in what happens when one of its target organs, the thyroid gland, is under- or over-stimulated. Without sufficient TSH, the thyroid gland soon shrivels, with dramatic effect. A diminished thyroid causes the human engine to slow down. The skin dries out, hair thins, the body puffs out as cells flood with water, behavior becomes listless and sluggish, and the mind deteriorates. If, on the other hand, too much TSH reaches the thyroid, the body begins to burn itself up. Food may be wolfed down, but the flesh nonetheless melts away. The body seeks in vain to sweat away its excessive heat; the heart pounds, the hands tremble, the eyes seem about to burst out of the skull.

When the pituitary operates smoothly—which, fortunately, it almost always does—FSH and LH work to perpetuate the species by signaling the glands in the male testicles to produce sperm cells and the male hormone testosterone, and by stimulating the female to produce a single mature egg each month. When FSH reaches the ovaries, it helps the follicle (or egg sac) to grow in the early stages of a woman's menstrual cycle. This follicle also releases estrogen, a female hormone, at mid-cycle, which serves as the feedback signal to the pituitary, prompting it to release just enough LH to cause the follicle to rupture and release its egg. Unless this sequence unfolds properly, a woman will become infertile. Later, if the female gives birth, PRL will tell the breasts to commence producing milk, and suckling will induce the pituitary to increase PRL secretion. However, if PRL is released at an inappropriate time, it can cause anovulation (failure to ovulate) or amenorrhea (failure to menstruate) or both. It can also cause inappropriate milk production.

While the pituitary gland is indeed wonderful, no one has ever claimed it to be endowed with a sense of humor. Yet it plays the major role in a fundamental practical joke on the human male, a joke remarked on at least since the time of Shakespeare: the relationship between the male sex urge and alcohol. As described by

the porter in Shakespeare's *Macbeth*, alcohol "...provokes and unprovokes: it provokes the desire, but it takes away the performance. Therefore, much drink may be said to be an equivocator with lechery: it makes him, and it mars him; it sets him on, and it takes him off; it persuades him, and disheartens him." We now know why. When alcohol reaches the male gonadal tissue in the testicles, biochemical processes that ordinarily would be devoted to making the male hormone testosterone are diverted into breaking down alcohol. This lowers the body's testosterone level. The pituitary detects this decrease and responds by producing more LH, thus signaling the testes to step up production of testosterone. Desire thus increases by the same mechanism that denies performance. Subjectively, not very funny. But objectively, perhaps one of nature's better practical jokes.

Perhaps the most spectacular pituitary hormone is HGH, human growth hormone. Unlike the other anterior pituitary hormones except PRL, growth hormone acts directly on a body function instead of through another gland. Given the right amount of Growth Hormone Releasing Factor (GHRF) sent from the hypothalamus and proper secretion of HGH from the pituitary, we grow to a stature dictated by our genetic heritage and by the nutritional and other environmental conditions encountered during infancy and childhood. But regardless of genetic endowment or favorable environment, a child whose pituitary fails to supply sufficient HGH will become a dwarf. The 31-inch "General Tom Thumb" (Charles Stratton), who was a major attraction in P.T. Barnum's circus, is considered an extreme example of HGH deficiency.

On the other hand, when there is too much HGH, growth fails to stop, and the child turns into a giant. If excess HGH is produced during adult life, the skeleton, then consisting of bones fully formed and hardened, can no longer respond. But the extremities—the hands, feet and chin—can grow, and do, swelling out into grotesque proportions in a condition called acromegaly, Greek for "large extremities."

Those who despair of progress in human relations might reflect on a

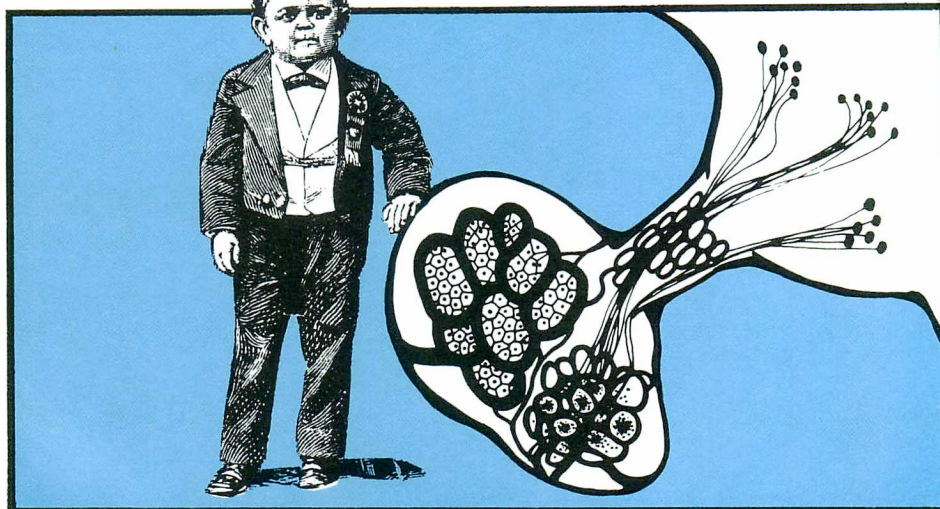
letter to *Time* magazine by the great American neurosurgeon Harvey Cushing, who carried out pioneer work on the function of the pituitary. Dr. Cushing took exception to a photograph of a woman captioned "Uglies," pointing out that she had been a pretty, vigorous woman until a malfunctioning pituitary produced acromegaly. He added that *Time* should not "...be frivolous over the tragedies of disease."

When Cushing was in London to receive an honorary degree, he requested permission to examine the skull of Byrne, the storied Irish giant, whose skeleton was displayed in the museum of the Royal College of Surgeons. When he stuck his finger into the base of Byrne's skull, Cushing found, just as he had expected, clear evidence of a tumor or other pituitary disorder.

As with any regulator or thermostat, the pituitary may produce too little (hypofunction) or too much (hyperfunction). If a condition called panhypopituitarism occurs, the impact of insufficient production will be felt on all the glands controlled by the pituitary. Too little of the hormone ACTH and the adrenal gland can no longer protect against stress and infection; too little FSH and LH and the female can no longer conceive; too little in the male and there is impotence; too little HGH and the result is hypoglycemia (insufficient sugar and hence insufficient energy source in the blood) and a drastic curtailment of growth.

We have already seen what happens when there is too little TSH. A pituitary with excessive hormonal output has equally dramatic though opposite impact on the body, such as the gigantism or acromegaly from too much HGH. For example, when the pituitary produces too much ACTH, a condition called Cushing's disease ensues. The body retains excess salt and water, the face bloats out into a characteristic moon shape, the upper body labors under rolls of fat, including a characteristic pad—the "buffalo hump"—between the shoulder blades, and loss of muscle in legs and arms makes them weak and spindly.

Pituitary hyperfunction may result from such causes as fungus infection, tumors and infarction (blocked or



congested blood supply). Pituitary tumors are now treated by microsurgery or radiation. Hormonal *deficiencies*—hypopituitarism—can now be dealt with by supplying an adequate quantity of the missing or insufficient hormone. This is not without its dangers, however, since it is difficult to determine exactly how much hormone is required. For example, in cases of infertility, the drug Clomid (clomiphene citrate) can stimulate the pituitary into secreting more FSH and LH. Statistics show that women who take Clomid and become pregnant deliver more than one child in 7 to 10 percent of the births, compared to 1 percent in the population as a whole. These multiple births result from ovaries overstimulated by the pituitary hormones so that more than one egg may be ripe and ready for fertilization at the midcycle time of ovulation.

Caution about stimulating or enhancing the production of pituitary hormones is particularly appropriate now that the technique of genetic engineering has created bacteria capable of producing the equivalent of the growth hormone HGH. This HGH equivalent, not yet approved by FDA for general marketing, is currently being given to over 3,000 American children in a carefully controlled research program. Since this hormone differs from many others in being species-specific (only HGH from a human source will do), HGH deficiency until recently required use of the minute quantities secured from autopsies. The supply was therefore extremely limited, the cost high. The new source of HGH is viewed as one of the most important

events in endocrinology over the last 15 years. It is of potential benefit to the estimated 10,000 American children suffering from pituitary dwarfism.

However, there is fear that the availability of HGH may produce a rush to inappropriate and unneeded treatment, such as to extend otherwise normal growth. This could prove dangerous since research already shows that elevated levels of blood sugar can accompany treatment with genetically engineered HGH. When measured against the potential benefit to children suffering from pituitary dwarfism from insufficient HGH, physicians, parents and the children may feel this is a risk well worth taking.

But for other children, who have a normal supply of HGH and who are below normal (or desired) height because of heredity or what is called psychosocial dwarfism—slowed growth due to stress—there is the danger not only of hyperglycemia but, at least theoretically, of atherosclerosis (thickening and hardening of the walls of arteries) or even acromegaly. That is why Dr. Alfred M. Bongiovanni, professor of pediatrics at the University of Pennsylvania, warns against abusing HGH and emphasizes the importance of very careful and thorough diagnosis to be sure that the treatment is given only to children suffering from pituitary dwarfism.

In the Old Testament psalm attributed to David, he rejoices, saying, "I am fearfully and wonderfully made." There can be few better proofs than the pituitary wonder within.

Tim Larkin is a freelance writer.



There's Rejoicing Over Re-joints

by Annabel Hecht

“Neither surgeons nor engineers will ever make an artificial hip joint which will last thirty years and at some time in this period enable the patient to play football.”

So wrote Dr. John Charnley, the pioneering British orthopedic surgeon, in 1961. New designs and new materials, some of them recently approved by FDA, may prove the first part of Charnley's prediction wrong. But everyone knows patients with artificial hip joints will never play football, particularly since three out of five are 65 or older.

Artificial hips may not create instant athletes, but they have brought relief to hundreds of thousands of people once crippled by arthritis and enabled them to live productive, pain-free lives.

Hips are by no means the only joints that can be replaced. Artificial knee joints are becoming increasingly common. Elbow, ankle, shoulder, toe, and finger joints are also replaced, although not as frequently as the hip and knee. Operations to replace joints—technically called arthroplasty—are performed primarily to relieve pain and secondarily to improve function.

The total number of arthroplasties performed is not known. A frequently cited number for hip replacements is 75,000 annually, although some place the figure at 100,000. According to Dr. William P. Fortune, orthopedic surgeon at George Washington University School of Medicine in Washington, D.C., the ratio of hip replacements to knee replacements is 2 to 1 and the ratio of hips to ankles is 30 to 1. Thus, these three types of joint replacements alone total 115,000 to 153,000 a year.

Artificial joints are regulated by FDA under the Medical Device Amendments of 1976. In 1982 the agency issued “generic” classifications for 49 types of joint replacements, including three for ankles, four for elbows, four for fingers, 12 for hips, 12 for knees, five for shoulders, two for toes, and seven for wrists. About half were put in the regulatory category calling for performance standards and half were put in the category requiring premarket approval before the device can go on the market.

The first joint to be totally replaced was the hip, anatomically the best place to start, since the hip is a simple ball-and-socket joint. One of the most commonly

used hip joint replacements today is just that—a ball-and-socket joint. The head of the femur (thigh bone) is removed, and a metal device consisting of a stem topped by a ball is cemented into the shaft of the bone. This is called the femoral component. The femur fits into a socket in the pelvis called the acetabulum. The artificial socket is called the acetabular component.

Variations on this basic design include femoral components that are tapered so that they fit snugly without cement. In one type of device the two components are linked together. In another, the femoral component terminates in a trunnion, or pin, that fits into the ball part, allowing the head to rotate on the stem. Interchangeable heads are available to allow for differences in the size of patients. Since it is not always necessary to replace both parts of the hip joint, separate femoral and acetabular components are available.

The materials from which these components are made must be extremely durable, since they must withstand a load actually equal to three to five times the patient's body weight with each step. Cobalt or titanium-based alloys or stainless steel is used for the femoral component, while high-molecular-weight polyethylene or, occasionally, metal is usually the material from which the acetabular cup is made. Late in 1982 this list was broadened to include ceramics—not the kind dishes are made of, but a material compounded of aluminum oxide. FDA approved two hip replacement systems with ceramic components, one to be cemented in place, the other not. Each consists of a cobalt-chrome alloy femoral stem, a ceramic head, and a ceramic acetabular cup.

To Dr. John Charnley, quoted above, goes much of the credit for the development of the total hip joint replacement used today. He was not, however, the first to come up with such an artificial joint. An ivory ball and socket had been implanted in a hip by a German surgeon in 1890.

At the turn of the century many European and American surgeons repaired damaged hips and other joints by padding the surfaces of the joints with a variety of materials, including fibrous tissue, celluloid, silver plates, rubber sheets, and even pigs' bladders.

With the development of corrosion-resistant material in the 1930s and biologically acceptable plastics in the 1940s

and 1950s, real progress in artificial joints could be made. The concept was explored of replacing the femoral head with a device that could move freely in the acetabulum. Unfortunately, many of these early devices became loose on the thigh bone or migrated within the pelvis.

Charnley's contribution was his discovery of low-friction arthroplasty. By coupling the smallest diameter ball possible on the femoral component with a socket made from a compound with the least potential for friction, he created an artificial joint that was efficient, durable and moved with ease. Charnley also was the first to use a newly discovered cement made of polymethylmethacrylate, which fixed the femoral component more securely to the bone and thus avoided the loosening that had plagued previous implants.

The new cement is cold-curing or self-curing and is approved by FDA for use in the United States. It is easy to apply, and because its mechanical properties differ from those of the bone and of the metallic implant, it serves as a buffer to absorb the stresses to which the joint is subjected. Still, it is the weakest link in the bone-cement-implant structure. Eventually the cement breaks down, causing the femoral implant to loosen.

This may no longer be a problem, however, since FDA has recently approved a total hip prosthesis that doesn't need cement to be fixed in place. Instead, the stem of the femoral component has a porous coating of tiny metal beads ranging in diameter from 150 to 400 micrometers. The beads allow the surrounding tissue to grow into the prosthesis, making it a part of the body.

One disadvantage of the new prosthesis, called the "Porocoat Modified Austin-Moore Total Hip Prosthesis," is that it takes longer for the patient to be up and around than with the standard hip joint replacement. Since time is needed to allow the ingrowth to take place, the patient's activity may be limited up to six months after the operation in contrast to the three months usually required for recuperation following an operation using the cemented-type prosthesis.

At this point no one knows how well the new prosthesis will hold up over time. Some of the cemented devices have served well for more than 10 years. FDA is therefore requiring postmarket surveillance for five years after implantation for all patients identified in the firm's premarket approval application.

Originally, total hip joints were implanted to relieve pain in arthritic patients over 65 years of age, and these patients receive about 60 percent of the implants annually. Because of the success of the operation, it is now available to younger patients, including teenagers, with hip problems. The most common reasons for total hip replacements in the elderly are osteoarthritis (60 percent), fracture-dislocations (11 percent), rheumatoid arthritis (7 percent), and aseptic bone necrosis (7 percent).

According to the Arthritis Foundation, the success rate for artificial hips is about 95 percent. Early complications

that may develop include infection, which occurs in about 1 percent of the hip operations, as well as dislocation and abnormal bone formation. Fracture of the femur or acetabulum may also occur. Blood clots are another problem encountered.

Failure of the hip replacement at later dates can be caused by loosening of the cement, fractures of the component, and just plain wear.

If the hip replacement fails, a second operation can be done, but it is generally less successful than the first time around. About 6 percent of the hip operations each year are revisions of previous surgery. If failure is due to infection, it may mean that the second implantation will have to be delayed until the problem is cleared up. If it is not possible to implant a second artificial joint, the hip may have to be immobilized.

There is another form of hip arthroplasty in which the joint is resurfaced rather than replaced. The top of the thigh bone is simply scraped and capped with a metal head, while the socket of the hip is cleaned and lined with plastic. Although it is a less radical procedure, resurfacing doesn't seem to have any advantage over the conventional joint replacement. Failures due to loosening of the prosthetic parts and fracture of the femoral neck have been reported, according to a 1982 consensus conference held at the National Institutes of Health.

Total hip replacement is not for everyone with painful joints. Patients with an active infection of the hip or bladder or any condition that destroys bone, such as a tumor, would not be candidates for this type of surgery. Complications such as heart disease or respiratory problems and excess weight also make some people poor risks for surgery.

Like hip joints, knee joints are replaced to relieve the pain of arthritis or osteoarthritis, improve the range of motion, and correct deformities. Although they are affected by arthritis more often than hip joints, knee joints are replaced less often.

Replacing the knee joint is not as easy as replacing a hip. Anatomically, the knee may look like a hinge, but it is considerably more complicated than that. Bending and straightening the knee involves rolling, rocking, sliding and gliding motions around a variable axis. Stability is provided by the surrounding ligaments and muscles.

Early attempts at knee arthroplasty in the 1940s used metal molds to cover the condyles (ends of the femur). Unfortunately, such devices did not relieve the patient's pain and were subject to loosening. The next decade saw the development of hinged knee joints, but these, too, had high failure rates. And, of course, the hinge could not duplicate the complex motion of the natural knee.

The real breakthrough in knee joint replacement came in 1968 when an associate of Charnley developed a prosthesis embodying the low-friction concept. Called a polycentric prosthesis, the new device consisted of two arc-shaped metallic runners, cemented into the ends of the femur, that moved in two polyethylene tracks cemented

into the ends of the tibia (lower leg bone). This design allows a nearly normal range of knee movement.

The polycentric device was soon followed by the geometric prosthesis, in which the two "runners" of the femoral component are joined, as are the tracking surfaces of the tibial component. With this device only two, rather than four, components need to be inserted.

During the past decade many new variations on these basic designs have been made. However, the quest for the perfect knee joint replacement goes on.

The knee joint prostheses currently available vary in design from non-constrained and semi-constrained devices, which depend on the surrounding muscles and ligaments for stability, to the totally constrained device in which the two parts are joined by a hinge.

Examples of less constrained devices—that is, those that permit nearly normal knee movement—include the polycentric design and prostheses that in effect resurface the joint with metal and plastic components fastened in place with the polymethylmethacrylate cement. In some cases the patella, or kneecap, is resurfaced as well as the ends of the femur and tibia. The hinge, still used in cases where destruction or deformity of the knee is severe, is an example of a constrained device.

Severe, almost incapacitating pain is the primary reason most patients seek knee joint replacements. At first only patients with rheumatoid arthritis had such operations. Now patients with osteoarthritis as well as other types of knee damage are also candidates. Knee joints are usually replaced in older patients, those in their 60s, and in those who won't be putting too great a strain on the device. A person who does heavy manual labor probably wouldn't be considered for knee arthroplasty. Joints replaced in younger, more active patients, say in their 30s, often aren't successful.

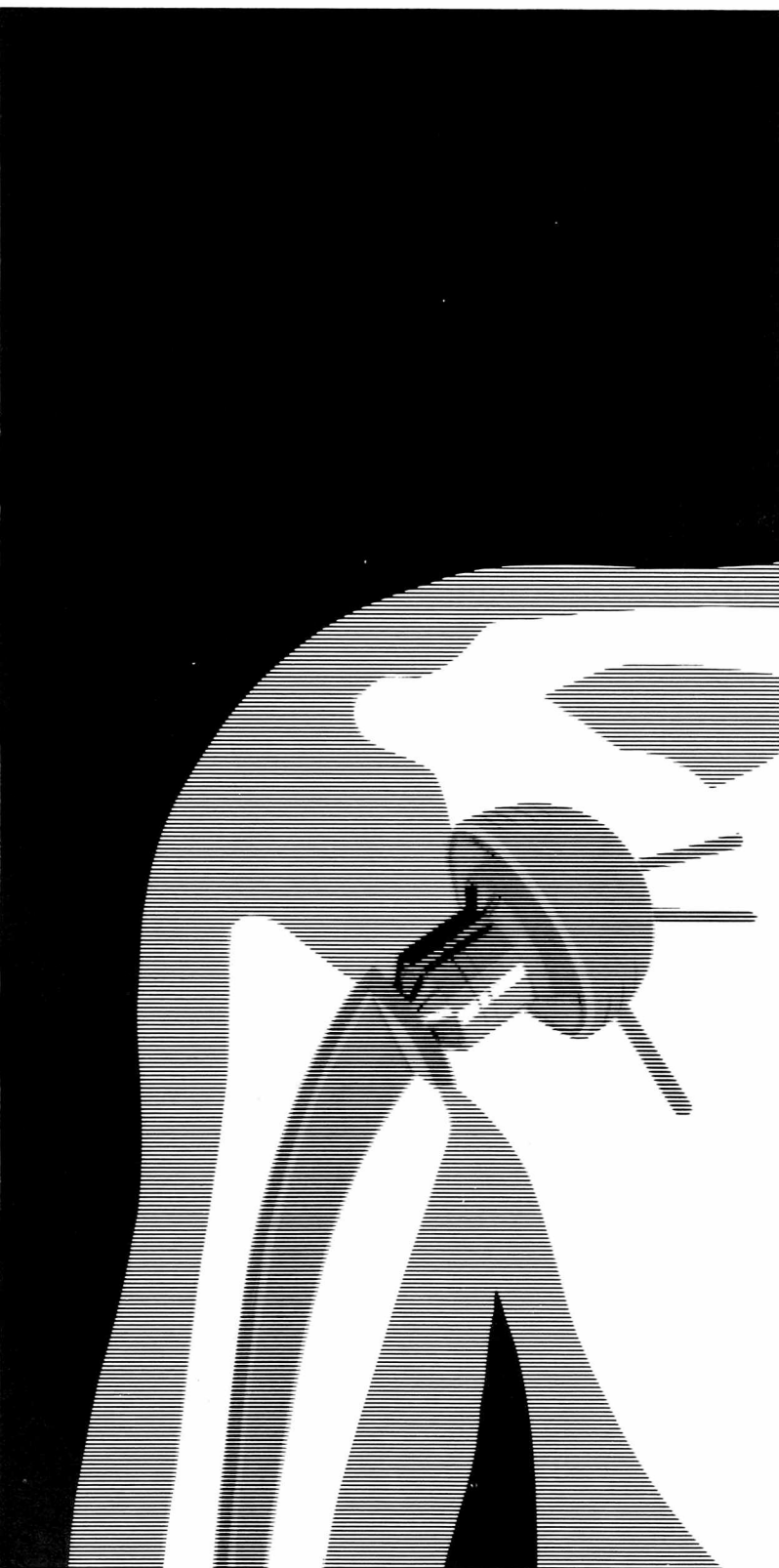
Other people who are generally ineligible for total knee arthroplasty include those with poor general health, obesity, infection, bone loss, bone thinning, and excessive deformity.

Infection and blood clots are the most serious complications following knee joint replacement operations, and special precautions are taken both before and after the operation to prevent them. Loosening of the prosthesis and dislocation of the joint also may occur. Unfortunately, artificial knee joints can't be replaced as easily as hip joints that go wrong. If it is necessary to remove an artificial knee joint, the natural joint may have to be fused, leaving the patient with a stiff leg.

Another joint in the lower extremities that can be replaced is the ankle. One of the simpler joints in the body, the ankle is very stable and has a small range of motion compared to the larger joints. For all that, ankles are subjected to tremendous compressive forces, at times equal to five times the body weight.

The ankle joint is not particularly prone to disabling diseases. Primary degenerative disease (osteoarthritis) is rarely seen in this joint; however, rheumatoid arthritis





and post-traumatic degenerative disease following ankle fractures do occur. A common method of relieving the pain of these conditions has been fusion of the joint. The fusion procedure has been so successful that ankle arthroplasty is not often performed. In fact, ankle replacement is usually recommended only for patients with rheumatoid arthritis and patients older than 60 suffering from arthritis following an injury.

Ankle joint prostheses generally are polyethylene and stainless steel components that replace the surfaces of the tibia and the talus, the top bone in the ankle. The tibial component fits over the dome-shaped talar component like a roller bearing.

Barring complications, such as delayed wound healing, the patient is usually hospitalized 8 to 12 days and can walk unaided 6 to 12 weeks after surgery.

The big toe is the only joint in the foot considered suitable for total replacement. This is usually done to relieve the pain of osteoarthritis, rheumatoid arthritis, and deformity caused by displacement of the big toe. The toe joint replacement is made of silicone elastomer (a flexible plastic) or a polyester-reinforced silicone elastomer that is soft and pliable and is not cemented in place.

At the other end of the anatomy, replacements are available for the shoulder, elbow, wrist and finger joints, but are implanted much less frequently than the artificial joints in the lower extremities. One reason is that need for replacement isn't as great. The upper extremity joints aren't subjected to the kind of pressures put upon the weight-bearing joints of the hips, knees and ankles. Pain and disability can be treated in other ways, such as splinting, medication, or physiotherapy. Unaffected joints can often compensate for the loss of function in other joints.

In addition, the complexities of these joints make it difficult to devise replacements that are totally effective. The shoulder, for instance, is the most mobile of all the joints, yet it is unstable. It behaves like a ball-and-socket joint, but the two components do not fit together like the ball and socket of the hip joint. The shoulder socket component, called the glenoid cavity, located at the upper edge of the shoulder blade (scapula), is more flat than cup-shaped. The head of the humerus (upper arm bone) is held against this surface by the rotator cuff, a band of intermingled muscle and tendon fibers. The interaction of this cuff with the deltoid (shoulder) muscle is what makes the shoulder function.

Although there is not much call for shoulder joint replacements, there are a few patients severely disabled by rheumatoid arthritis who may benefit. The operation involves replacing the head of the humerus with a component made of alloys such as cobalt-chromium-molybdenum and resurfacing the glenoid cavity with a similar alloy or ultra-high-molecular-weight polyethylene.

Both components are fixed in place with polymethylmethacrylate cement.

FDA's "generic" classification of shoulder joint prostheses includes a constrained device, in which the two components are joined, a non-constrained device with no linkage across the joint, and a semi-constrained device in which the humeral head is replaced with a metal alloy. The classification also includes replacements for the glenoid and humeral components separately.

Complications that have been reported with these prostheses include infection, dislocation of the components, fracture of the scapula, and fracture of the humeral component.

Replacing the elbow joint presents still another set of problems. The elbow is not the simple hinge it appears to be. It is not even a single joint but is composed of three sections, involving the three arm bones that meet at that point: the humerus in the upper arm, and the radius and ulna, the bones of the forearm. Each section of the joint has a different stress bearing and different rotational function.

The earliest elbow joint replacements were constrained, or hinged, devices that required removal of the lower end of the humerus and sometimes a portion of the ulna for implantation. Although they provided stability, they had some serious complications, including loosening of the device and bone erosion and resorption, resulting in fracture of the bone around the device and difficulty in salvaging the bone if the device had to be removed.

Better results have been obtained with semi-constrained elbow joints—i.e., those in which the two components are not linked. The "generic" device classified by FDA consists of a humeral resurfacing component made of a cobalt-chromium-molybdenum alloy and a radial resurfacing component of ultra-strong polyethylene, both fixed in place with polymethylmethacrylate cement.

Two single-joint prostheses are included in FDA's classification. One is a medical grade silicone elastomer device intended to replace the head of the radius. Experience with this type of device has shown that it can relieve pain and increase the range of motion of the elbow. The other type of elbow joint, an uncemented metal alloy replacement for the end of the humerus, has not been as successful in relieving pain and is more prone to complications, such as dislocation and blockage of motion because of new bone growth.

Elbow joint replacement should be reserved for patients with painful limitation of motion caused by rheumatoid arthritis, trauma, or infectious arthritis for whom regaining motion is more important than gaining strength and stability.

The wrist is a key joint in the upper extremity. It is made up of eight bones, called the carpals, arranged approximately in two rows. The proper balance of the wrist

system depends on the shape of the bones and the integrity of the ligaments that hold them all together. If anything happens to those ligaments, the system collapses. Rheumatoid arthritis is a frequent cause of wrist deformity.

Wrist problems can sometimes be solved by fusing the joints, but if the patient has other deformities of the arm or shoulder it may be necessary to preserve some motion in the wrist itself.

A common type of implant for damaged wrists is a one-piece device made of silicone elastomer designed to replace the lunate, scaphoid or trapezium bones in the wrist. Another type of wrist joint replacement consists of a single across-the-joint linkage made of polyester-reinforced silicone elastomer, used without cement.

Two types of metal wrist joint replacements are the across-the-joint (or linked), constrained device and the non-linked, semi-constrained device. The latter may be either a one-part radial component made of a metal alloy with a polyethylene bearing surface or a two-part radial component consisting of a metal stem mounted by a polyethylene ball matched with a metal metacarpal component.

Nowhere else are the ravages of rheumatic diseases more visible than in the hands. The metacarpophalangeal joints (those involving the hand and finger bones) are classically affected by rheumatoid arthritis. The severe deformity often seen in victims of this disease is the result of a combination of joint destruction and soft-tissue contraction.

Fortunately, for many such patients the pain and deformity may be relieved with artificial finger joints. A common finger joint prosthesis is a single flexible, across-the-joint component made from either a silicone elastomer or a combination of polypropylene and polyester material. The whole device may be covered with a silicone rubber sleeve. Such artificial joints may be used to replace either the metacarpophalangeal, or first finger, joints. One problem with such implants is that they can fracture, leading to inflammation of the joint from bits of plastic.

Constrained, across-the-joint models consisting of two metal components or a metal and a polyethylene component also are available for finger joint replacement. Bone erosion, loosening of the prosthesis, and joint deformity are some of the complications associated with these joints.

While arthroplasty is becoming a commonplace operation and is, for the most part, successful, patients should realize that such surgery is not without some risk. Joint replacement is not a cure for arthritis. Furthermore, artificial joints are never as strong as the real thing and must always be treated with respect.

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

First Hand Knee Account

by Freda Corwin

When you're feeling fit and have the energy to take brisk, five-mile walks nearly every day, the thought that you may be immobilized by an arthritic knee seems unthinkable. I'm old enough to know that few of us can escape the infirmities brought on by the body's normal wear and tear, but it never occurred to me that active me would be a candidate for a total knee replacement. Yet, I was operated on in the fall of 1983, and became one of the many thousands of men and women in the United States each year to have total knee replacements, the honors being about evenly divided between the sexes.

I have always resisted going to doctors. I believe most of the things that ail you get better in time if you have the patience to let nature take its course. But not this time. Increasing pain in my right knee made me change my mind. I looked around for an orthopedist skilled in joint diseases. My friends were sure they had just the right man for me. I wound up with an impressive list of doctors, including the joints specialist for the Washington Redskins football team. Having decided on one, the first order of business was a series of X-rays, including an arthrogram, in which a dye is injected into the knee joint. My condition was diagnosed as osteoarthritis, a degenerative joint disease that in my case resulted in the erosion of cartilage of the knee joint. The radiology report said the meniscal cartilage was ruptured, apparently making conventional surgical repair impossible.

This had happened in the fall of 1979. For the next four years,

various treatments were prescribed—bed rest, anti-inflammatory medications, exercise, hot and cold applications, cortisone injections, aspirin. Only temporary relief resulted.

I had read enough about arthritis to know that no cure has yet been discovered for this disease which afflicts upward of 20 million Americans in so many different ways. Since none of the treatments seemed to work, and the pain had intensified to the point that I had great difficulty walking two blocks to the supermarket, I decided to consider surgery.

This led me to Dr. William P. Fortune, of the George Washington University School of Medicine in Washington, D.C., a pioneer in joint surgery. After further X-rays I was told that a knee replacement would not only relieve me of pain, but also help correct a bowing in the leg caused by the osteoarthritis.

I was asked to think it over. I was aware that at my age (70 plus) major surgery could be a problem and would require a long convalescence. I also knew that knee replacements are not as successful as hip replacements because the knee is a much more complicated joint. In Dr. Fortune's words, the knee is not a hinge joint but a machine that changes its fulcrum of motion—rolling, rocking, sliding and gliding.

I didn't take long to make up my mind to have the operation. I entered the hospital two days before the surgery for additional tests and to adjust to my new environment for the next three weeks.

I found on my night table a copy of an illustrated article from a medical journal describing in explicit anatomical detail just what was to be done to my knee—what was to be removed, and what put in and where. Some patients may not want to know the details—but the hospital assumed, and I think correctly, that every patient has a right to be fully informed. After reading the article, I felt fully informed but suspected that

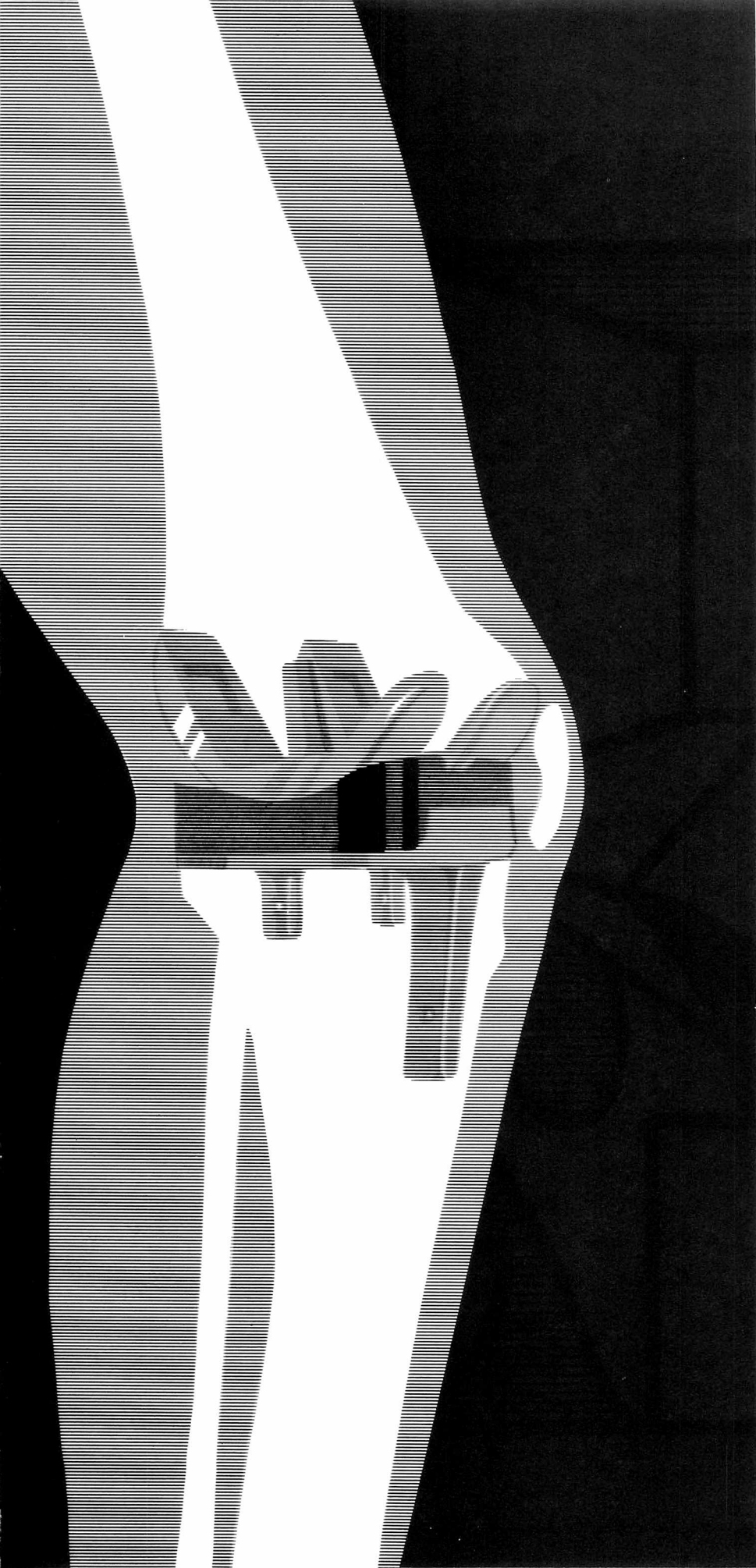
somehow I would no longer be able to see the humor in those old cracks about housemaid's knee and water on the knee.

The operation under general anesthesia lasted more than two hours. It included resurfacing of abnormal surfaces of the knee joint—namely, the lower thigh bone (femur), the upper shin bone (tibia), and the underside of the kneecap (patella). The resurfacing components can be plastic or metal, held in place by a special cement. Additional hardware, such as some small pegs and a screw, is used for further reinforcement.

Afterward, I was returned to my room on the orthopedic floor. The major concerns now were to guard against infection (with antibiotics administered intravenously and then orally), to be on the alert for blood clots, and to carry out a system of exercises.

To prevent clots, I was given a blood thinner (warfarin), required to wear an elastic thigh-length stocking to control circulation in the lower limb, and to use, several times a day, a breathing exercise incentive device to clear the lungs and to increase blood flow.

As a further precaution against blood clotting, I volunteered to participate in a new research project to detect potentially dangerous clots, even before they start to form. The test consisted of injection into my vein of platelets treated with a radioactive tracer substance, Indium-111. The platelets had come from blood out of the hospital blood bank. The consent form I was required to sign said there is little risk of developing hepatitis and the radiation exposure is small—the equivalent of dosages received in many nuclear medicine procedures. After considering the benefits and risks, I decided to take the test. A day after the platelet injection I was placed under a camera loaded with film sensitive to Indium-111, and pictures were taken of the radioactive platelets in



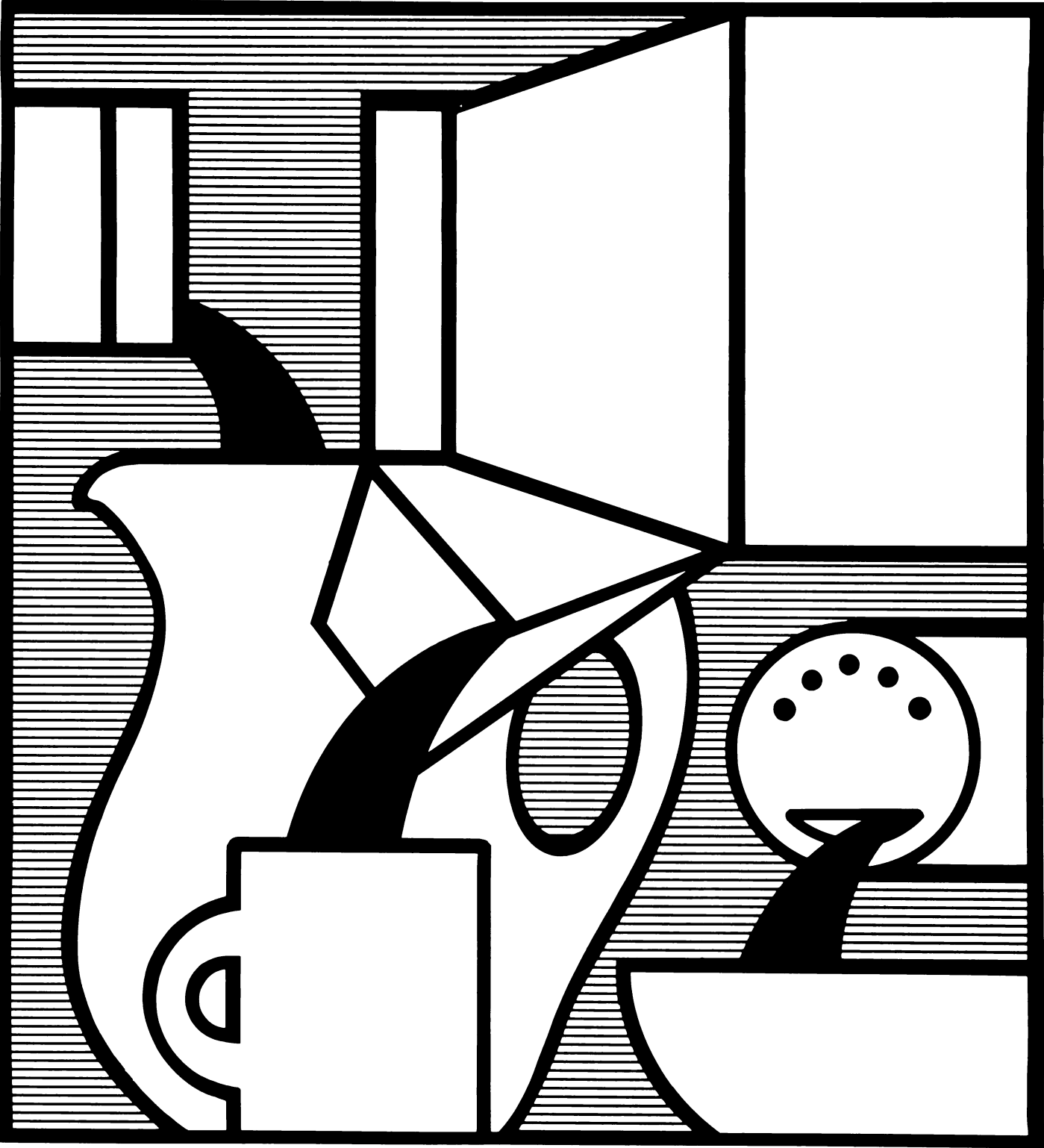
the bloodstream. The finished photos, unlike X-ray negatives, were printed on snapshot-size glossy paper. They showed no evidence of clots, but I had to continue to wear my white elastic hose and use the breathing device. The consent form told me that the records identifying me would be kept confidential should an FDA inspection of the blood bank take place.

Any doubts I had about the importance of exercise for a patient with a brand new knee were promptly dispelled when I saw two prominent signs taped to the sling exerciser over my bed. The first sign gave four-step directions for knee flexing, bending, heel lifting, etc. The second said: "Please, Mrs. Corwin is to ambulate at least qid." Translation: I was to walk four times a day. The signs reminded hospital personnel not to overlook an essential duty.

There was more. Every morning I was taken by wheelchair to join other orthopedic patients in exercises conducted by physical therapists. A drug taken beforehand helped alleviate the pain connected with this rather strenuous workout. One morning I was surprised to find in a wheelchair next to mine a well-known outpatient, Jim Brady, the President's press secretary. I learned he comes from his home to the hospital regularly for therapy. We exchanged pleasantries; it made my day.

I write this 10 weeks after my discharge from the hospital. There is still a stiffness in the joint due to a tightening of the healing tissues, and in bed I still must wear a knee immobilizer, a padded splint that resembles the shinguard worn by hockey goalies. But the bow in my leg has disappeared, and I walk without a cane and without pain. Will I be able to resume those long, brisk walks? Perhaps, but a little less briskly. I'll take it in stride.

Freda Corwin is the wife of Emil Corwin, a member of FDA's press staff.



On Making Food Labels Truthful

by Chris Lecos

Consumers do not always get what they think they are buying. Although the American food industry as a rule markets what it promises, there has always been a small number of entrepreneurs who cut corners illegally—by giving less than the declared weight on the label or by substituting cheaper ingredients than those a food shopper thinks are in the package.

For example, when buying orange juice, or apple juice or maple syrup, most shoppers take it for granted that this is indeed what they are getting. A shopper checking the label's ingredient list and finding the ingredients looked for will buy it with confidence that the label is truthful.

Unfortunately, that is not always the case, and economic deception is not only of concern to FDA but also to the responsible members of the food industry. Most of these believe such deceptive practices damage the industry's reputation and believability and give a competitive edge to the cheat, who can sell cheaper by cutting quantity or quality.

Such deception violates federal law—primarily the Food, Drug, and Cosmetic Act, which FDA enforces. As a protection to consumers, FDA has established many food standards specifying composition, makeup and labeling it requires for a wide variety of food products.

Although FDA's principal responsibility has always been to protect consumers from products harmful to public health, economic deception is covered in a number of ways. For example, a product violates the law if its net weight is below that given on the label. It may be considered adulterated or misbranded if certain ingredients are substituted illegally for those claimed, or if the labeling is false and misleading.

For the 1984 fiscal year, which began last Oct. 1, FDA officials in Washington, D.C., sent a directive to the agency's field offices advising them that FDA will "continue to emphasize its commitment to pursue legal actions where economic fraud is encountered." The result is that FDA's field investigators are looking for deceptive economic practices at the same time that they are checking food products for safety.

The directive states that since many economic deceptions are intentional, FDA's Bureau of Foods in Washington, D.C., is prepared to move quickly where a clear-cut case of economic fraud is demonstrated.

Although FDA field investigators are to be alert for any form of economic deception regardless of the product, the directive assigns a higher priority during inspections to certain food categories. In the case of product

substitutions, the agency listed the following food areas and indicated the types of adulterations that have been common in the past:

- Honey, maple syrup and sorghum products, in which fructose, invert or corn sugars are substituted wholly or in part for those the manufacturer claims for the products. Last year a federal grand jury in Jackson, Miss., returned a 13-count criminal indictment against two men for allegedly manufacturing, processing, shipping and selling foods in interstate commerce that were labeled falsely as maple syrup, honey and sorghum syrup products. FDA said the products contained corn or sugar syrup and were artificially flavored—in effect, were cheaper substitutes for the products they were claimed to be.
- Apple juices that have been adulterated and misbranded through the use of various sweeteners, water, apple flavoring, apple essence, and other ingredients.
- Orange juices that are being marketed as 100 percent orange juice but fail to meet FDA food standards because of the use of pulp-wash solids and other color and flavoring ingredients. These practices have aroused responsible members of the Florida citrus industry, which produces 90 percent of the nation's orange juices.
- Olive oil and sesame seed oil in which corn, soy and cottonseed oils are substituted.
- Breaded shrimp that is sold with less than the minimum of 50 percent shrimp material.
- Grated cheese that contains whey solids instead of Parmesan, Romano, or other cheese claimed on the label.
- Scallops that aren't scallops because they consist of cheaper fish fillets cut up to resemble scallops.

In searching for products with net weights less than declared weights, FDA's directive emphasizes these products: nuts, instant tea, instant coffee, spices, and overglazed seafood, especially rock lobster tails processed in Florida.

Glazing preserves frozen seafood by coating it with a layer of ice. Overglazing means the product is coated with too much ice and part of the weight of the ice is included in the declared net weight of the product. Although only the seafood is supposed to be included in the declared weight for the product, FDA has found up to 30 percent of the declared net weight to be glaze or ice weight.

Taylor M. Quinn, associate director for compliance in FDA's Bureau of Foods, said the noted food products are the ones the agency regards as the biggest problem. He said FDA has met with representatives of the apple,

citrus and honey industries because of the illicit practices of some industry members.

The extent of such economic violations is uncertain, although the general belief is that the problem is a selective one, Quinn said. "Violations tend to be cyclic," he continued, "and you can, in fact, find evidence of these kinds of violations all the way back to the turn of the century." With FDA's present staff and financial resources, he added: "All we can do is try to hold it down. We're looking into it so far as our resources will permit."

FDA can take three types of actions against economic deception: The agency can ask the food manufacturer to recall the product; it can seek legal action to seize and remove the product from the marketplace or, if the necessary evidence is substantial enough and the case warrants it, criminal action can be sought.

But prosecution is not always easy, for some companies use such sophisticated methods of adulterating their products that violations are difficult to prove. This is especially true for some adulterated orange juice, apple juice, and honey and maple syrup products.

FDA regulations define orange juice as a product derived from the unfermented juice of mature oranges. Some small seed fragments cannot be removed during the initial manufacturing process, but the larger seeds and "excess pulp" must be removed. If the label calls it "orange juice," the consumer is entitled to exactly that.

But orange juice comes in many varieties. FDA has separate standards for ordinary orange juice, and for orange juice that is pasteurized, canned, from concentrate (reconstituted), frozen concentrated, canned concentrated, for manufacturing purposes only, with preservative, concentrated for manufacturing, and concentrated with preservative (concentrate is juice with most of the water removed). Some products can legally contain sugars or other sweeteners if they are identified on the label.

During manufacture, some pulp from the initial juice extraction process can be added back to a product sold as orange juice or concentrated orange juice. The unused, excess pulp is not thrown away; instead, it is often stored in tanks and sold to firms making other kinds of beverages. It is usually referred to as washed or spent pulp or as pulp-wash solids. The washing process removes any remaining juice and sugars.

In some cases of adulteration, washed or spent pulp from other processors is used, along with other color and flavoring agents, to produce a product that is illegally labeled and sold as an orange juice product. Turmeric, a spice and powerful coloring agent not permitted in orange juice, is sometimes added to give the adulterated

products the appearance and taste of orange juice. Sugars and other sweeteners may also be added.

Adulteration of orange juices sometimes is hard to prove because the water, sugars and components added illegally are hard to distinguish from those naturally present in orange juice, according to Melvin R. Johnston, Ph.D., chief of FDA's plant and protein technology branch. "Analytically they are so similar to each other that chemists cannot always differentiate between them," he explained.

Some of FDA's problems were outlined in 1982 to a Senate subcommittee by former FDA Commissioner Arthur Hull Hayes Jr. after FDA was directed in 1981 to pursue a vigorous enforcement policy on any violations of federal food standards for orange juice products. In April 1981, FDA conducted a survey to determine whether processors of orange juice made from concentrate and frozen concentrated orange juice were adulterating these products with water, sugars, preservatives and orange pulp-wash solids and then labeling them as "100 percent pure orange juice" or as "orange juice concentrate" without any qualifying or ingredient declaration. This constitutes misbranding.

Of 13 firms inspected during the survey, six made products that had "minor deviations" from FDA food standards or labeling deficiencies. Three other firms were using illegal color additives and/or pulp-wash solids. As a result, FDA seized 10 lots of adulterated orange juice. Samples of orange juice from the seizures revealed the presence of turmeric. Four more firms were later inspected, including one in Mexico, and 12 more lots of orange juice adulterated with turmeric were found.

Hayes reported to Congress that the value of adulterated orange juice lots involved during these regulatory actions in the 1981 and 1982 fiscal years was estimated at nearly \$3 million.

The basic problem for FDA in cases of suspected adulteration, the report continued, is developing laboratory evidence strong enough to stand up in court. "The analytical methodology and procedures necessary to confirm suspected violations due to added orange pulp-wash solids and most sugars are not sufficiently established to be used in court, thus limiting any vigorous enforcement of the orange juice standards in resolving adulteration of orange juice from use of these substances," Hayes said.

The Florida citrus industry and the federal government have in recent years sought to improve their analytical methods for detecting adulteration, Hayes said, and he added: "Throughout this period of time, adulteration of

citrus juices has progressed from simple dilution with water, sugar and acids to sophisticated methods utilizing substances to obscure adulteration. As the analytical methods of detection have improved, so have the techniques of disguising adulteration become more sophisticated."

A regulatory device was hatched to thwart the adulterators. In April 1982 FDA approved a petition by Florida's Department of Citrus to permit the addition of the preservative sodium benzoate to orange pulp-wash solids without declaring the addition on a label. The Florida agency then published a regulation requiring orange pulp-wash solids to contain sodium benzoate. Thus, if the pulp-wash solids were used by some other firm to produce a fraudulent orange juice, the detection of sodium benzoate in the product would serve as evidence of adulteration. Sodium benzoate is permitted as a preservative in certain standardized orange juice products but not in single-strength (pure) orange juice or frozen concentrated orange juice.

In a further effort to catch cheats, FDA's Bureau of Foods stepped up its research on ways of confirming orange juice adulterations and proving them in court. Because orange juices vary by the kind of orange, the time of year and place grown, soil conditions, and other factors, identification is difficult.

FDA is taking samples of various orange juices produced in the United States, along with adulterated varieties that FDA itself is duplicating, and then subjecting the samples to analytical techniques in an effort to develop a profile or "fingerprint" or "pattern recognition" of what real orange juice is. The analytic methods being used include gas chromatography, high performance liquid chromatography, and the plasma emission spectrometric method. The data obtained are fed into computers to develop the profile. In recent years similar computerized pattern recognition methods have been used on wines and Scotch whisky and to identify sources of crude oil spills.

The first phase of the orange juice work was completed last June and involved 25 samples of authentic and adulterated juices. The second phase, now under way, involves 125 samples and will be followed by a phase of research in which a minimum of 500 samples of adulterated and authentic orange juices will be analyzed. The research project is scheduled to be completed in September 1985. Officials say the results so far have been "extremely promising."

Apple juice adulterations also are hard to detect sometimes, according to FDA officials. The juice usually is

adulterated by a combination of water, sweeteners, synthetic malic acid, apple flavoring, caramel color, and apple essence. Malic acid is a natural constituent of apple juice and contains only one biologically active chemical compound. Synthetic malic acid contains chemical compounds that are both biologically active and biologically inactive and, as a result, FDA scientists can detect when a synthetic acid is used. It also is possible to detect apple juice adulteration if the sugar ratios are out of line. Corn or cane sugar use is easy to detect, but some sophisticated operators sometimes switch to the harder-to-detect beet sugar.

FDA also plans to apply computerized pattern recognition analysis to apple juice adulterations and may expand this type of food analysis research into other food areas.

One of the more effective actions taken in recent years against apple juice adulterators was a suit brought by an industry group, the Processed Apple Institute, against some New York state operators. The suit resulted in an out-of-court settlement of nearly \$500,000, although the accused firms did not have to acknowledge any guilt. FDA also initiated seizure and recall actions.

The so-called "carbon 13-14" method is used to detect the illegal use of corn and cane sugar in honey and maple syrup adulterations as well as in orange and apple juice adulterations. In oversimplified terms, laboratory scientists are able to distinguish the sugars that are added from those that would be naturally present. When some operators started using invert and high-fructose sugars, scientists encountered greater difficulty in detecting adulterations until the carbon isotope method of detection was employed. The method was developed by a retired U.S. Department of Agriculture biochemist, Jonathan W. White Jr., Ph.D., who is regarded as one of the foremost experts on honey and maple syrups. However, it is not effective in detecting adulteration when beet sugars are employed.

The struggle against some food adulterators is never-ending. While FDA and other scientists strive to develop improved methods for detecting violators, they know from experience that companies that want to adulterate their products will be refining their own scientific tools. FDA's Melvin Johnston put it this way during a conference last June of food and drug officials on the detection of juice adulteration: "It's a good example of the science of enforcement becoming the science of adulteration."

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

Hunger Is More Than An Empty Stomach

by Carol L. Ballentine

Walk into any neighborhood drugstore and you'll probably find a shelf—or shelves—of products offered to “control appetite” or “curb hunger.” These days, thin is in and appetite seems to be the enemy—an ogre to be suppressed, if not eliminated, so that everyone can have a body that's a 10.

Yet appetite is an essential body function. Everyone needs to eat, and the appetite is what cues the body to take food.

But how exactly does the appetite work? Can it be chemically suppressed? And should it be tampered with?

Although it may be logical to assume the stomach is the controlling organ for hunger, it is not. The master control of the appetite lies at the center of the brain in an area called the hypothalamus. The hypothalamus integrates the functions of the nervous system and endocrine glands (including the thyroid, adrenal and pituitary glands). Besides stimulating “hunger pangs,” the hypothalamus has some control over a number of physiological functions, including growth, sexual activity, lactation, water balance, menstruation, and metabolism of carbohydrates, protein and fat.

Scientists have long known that the hypothalamus is a prime mover in the urge to eat. This was determined by classic studies of feeding behavior in rats. In those studies, certain areas of the hypothalamus in rats were either stimulated or destroyed. Destruction of one area—the ventromedial, or midregion, hypothalamus—induced considerable overeating and obesity; in contrast, stimulation of this area caused the rats to stop eating, even those previously unfed. When researchers made small lesions in another area—the outer, or lateral, hypothalamus—the rats stopped eating. Some of the animals starved to death, even though there was food in their cages. Stimulation of this same area, on the other hand, induced not only eating but licking,

chewing, salivating and active searching for food.

From these studies, some scientists have assumed that the hypothalamus contains a “satiety” (fullness) center and a “feeding” or “appetite” center. These centers are acted upon by various body chemicals that signal the need to eat and then stimulate “hunger pangs,” or recognition of the desire to eat. Scientists still don't understand exactly how this process works but they know what many of the chemicals are.

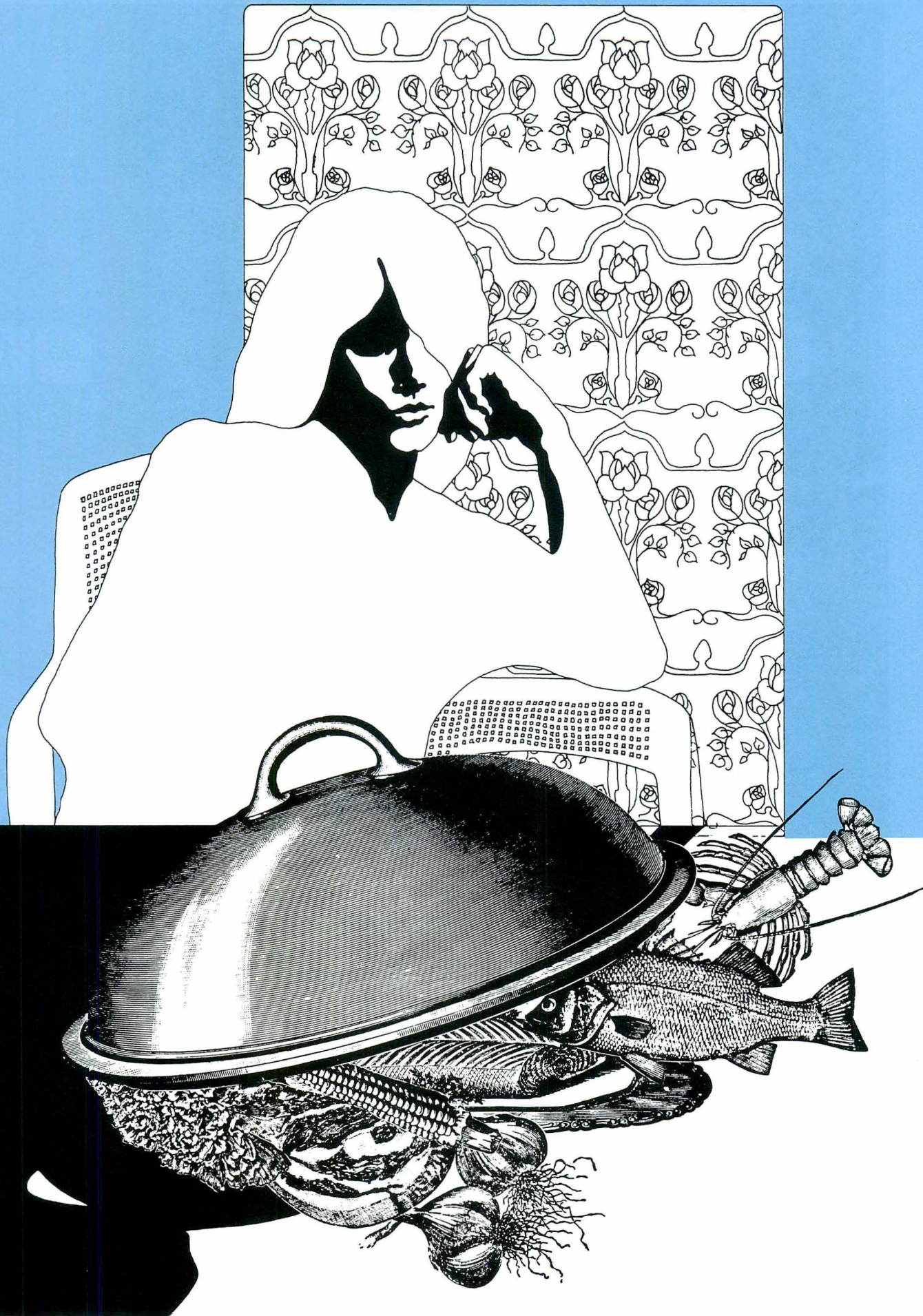
One of the first chemicals identified as giving such signals was glucose. Scientists have known since 1916 that when blood glucose to the brain gets low, a person gets hungry. When blood glucose rises—which happens when a person eats—appetite decreases. But how glucose acts in the brain to turn appetite on and off is still a subject of speculation.

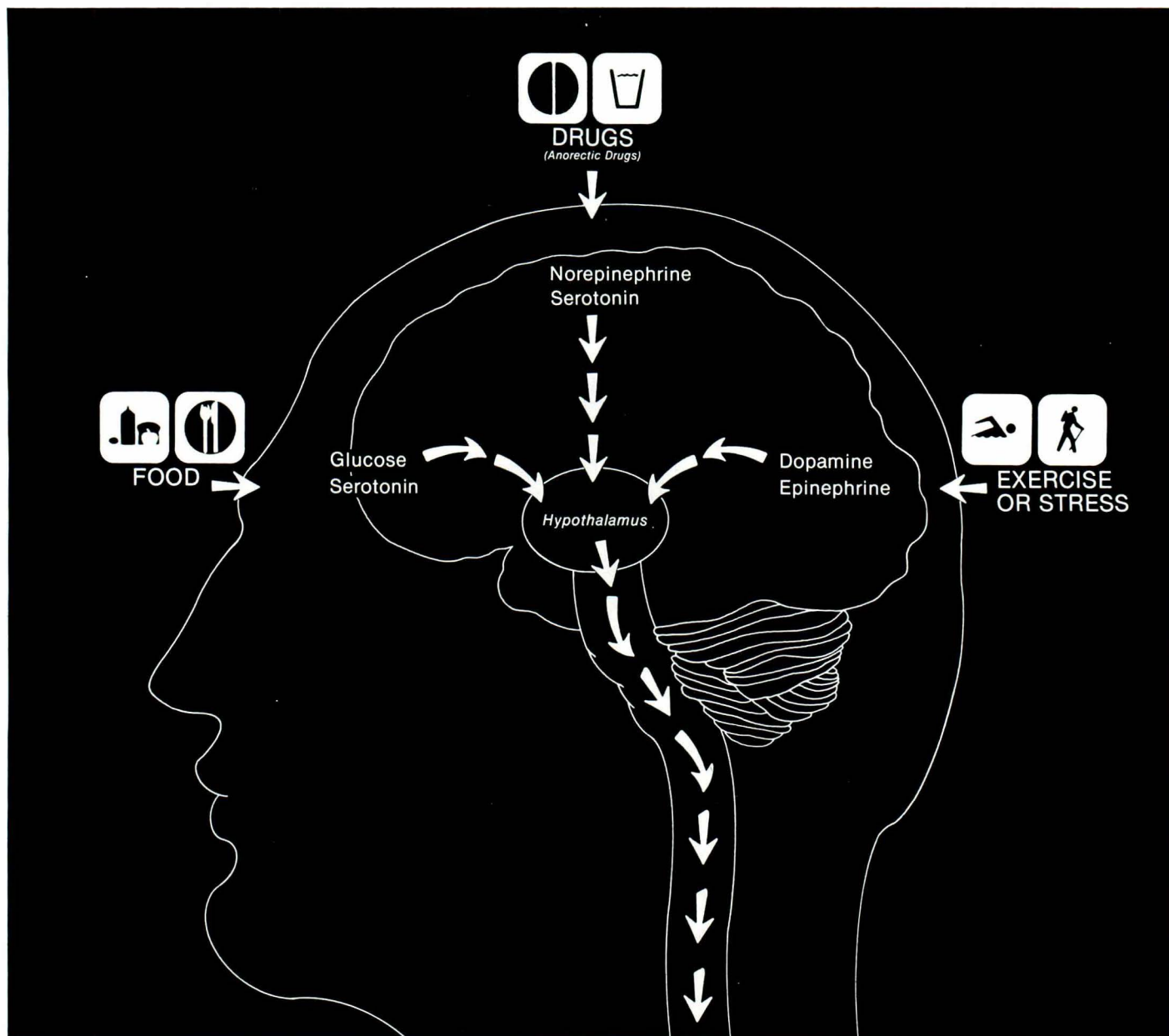
One theory is that there is some type of glucose receptor in the brain, possibly in the ventromedial hypothalamus (satiety center). Thus, the theory goes, eating causes blood glucose levels to rise, stimulating the firing of neurons in the satiety center. This suppresses the appetite center and inhibits eating.

Another theory is that high blood glucose levels prompt the release of insulin by the body. Appetite is curbed when insulin in blood plasma reaches a certain level. Regardless of the process, it seems to take time for glucose to act in the brain to cause satiety. That's why specialists advise people trying to lose weight to eat slowly.

Much current research on the physiological process of hunger involves chemicals called neurotransmitters, which transmit messages from nerves to other nerves or to muscles. Reduced appetite has been found when the brain has high levels of several neurotransmitters, including serotonin, norepinephrine, epinephrine and dopamine. With serotonin, low

(continued on page 28)





levels mean appetite increases.

It is the neurotransmitters that seem to be responsible for the loss of appetite caused by anorectic (appetite-suppressing) drugs. The first prescription drugs to be widely prescribed for appetite suppression were the amphetamines, central nervous system stimulants. However, amphetamines cause serious side effects as well as dependence, and they have gradually been replaced by newer and safer amphetamine-type drugs. Generally, these anorectic agents decrease appetite by stimulating the hypothalamus. According to the American Medical Association's reference book *AMA Drug Evaluations* (5th edition), the majority seem to facilitate the release of norepinephrine and dopamine; one (fenflura-

mine) is thought to decrease appetite by facilitating metabolism of serotonin.

Anorectic drugs affect more than just appetite; they can have dangerous side effects, including hypertension. However, there's hope for dieters whose physicians recommend appetite-suppressing drugs: Three federal government neuroscientists recently reported on studies suggesting that drugs free of such side effects may be developed.

The scientists—Steven M. Paul and Bridget Hulihan-Giblin of the National Institute of Mental Health, and Phil Skolnick of the National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases—have identified specific binding sites for amphetamine derivatives in the brains of rats.

According to Skolnick, the studies suggested very strongly that the binding sites, found predominantly in the hypothalamus, are involved in the appetite-suppressing action of amphetamines. If this is proved, it opens the possibility of developing an anorectic drug that will act only on these sites to reduce appetite without side effects.

Serotonin has been studied by researchers at the Massachusetts Institute of Technology. Based on these studies, Judith Wurtman, Ph.D., a research scientist in the MIT Department of Nutrition and Food Science, has suggested the existence in humans of a specific hunger for carbohydrates.

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Drugs And Your Waistline

In the world of products promoted as appetite suppressants, a person can get pretty confused trying to decide what works and what risks each involves. Here's a sampling of the more common products one might encounter on the way to seeking slimness:

- **Prescription anorectic agents** decrease appetite by stimulating the hypothalamus. These include amphetamines and newer drugs, which are chemically related to amphetamines but have fewer side effects. According to the American Medical Association's reference book *AMA Drug Evaluations* (5th edition), amphetamines are "not advocated for the treatment of obesity because the risk of dependence is great. The FDA Bureau of Drugs has concluded that the amphetamines have no advantage over other anorectic drugs that have less risk, and a few states have prohibited their use for weight control." Prescription anorectic drugs recommended for treatment of obesity include mazindol, phentermine, and diethylpropion. However, they are recommended in conjunction with other weight-loss regimens such as diet and exercise.

Side effects of prescription anorectics include nervousness, irritability, insomnia, blurred vision, dizziness, palpitations, hypertension, sweating, nausea, vomiting, and sometimes diarrhea or constipation.

- **Phenylpropanolamine (PPA)** is the active ingredient in most nonprescription weight-control products, such as Dexatrim, Appedrine, Control, Dietac, Prolamine and Adrinex. PPA is related chemically and pharmacologically to amphetamines and affects the cardiovascular and central nervous systems similarly, but to a lesser degree. Side effects include nervous-

ness, insomnia, headaches, nausea, tinnitus (ringing in the ears), and elevated blood pressure. People with high blood pressure or heart, thyroid or kidney disease should not take products with this ingredient except under the advice and supervision of a physician.

PPA is available in doses that equal 75 milligrams a day. In 1979, FDA's Advisory Review Panel on Over-the-Counter Miscellaneous Internal Drug Products, in its review of OTC weight-control products, said that PPA is safe and effective for short-term weight control (up to three months), but at dosages of 25 to 50 milligrams three times a day—that is, 75 to 150 milligrams a day.

Studies made available after the panel's report was submitted, however, have shown that doses of PPA higher than 75 milligrams may cause a serious elevation in blood pressure. Until FDA completes its review of these findings, the agency will not permit PPA to be marketed at a dosage level higher than 75 milligrams per day.

- **Benzocaine**, the active ingredient in AYDS candy and dietetic lozenges and gum, is a topical anesthetic said to work by anesthetizing the tongue, reducing the ability to taste foods. Benzocaine is one of two nonprescription ingredients found safe and effective by the FDA advisory panel that reviewed OTC weight-reducing ingredients. Animal and human studies reviewed by the panel indicated that use of benzocaine-containing products contributes to weight loss. According to *AMA Drug Evaluations*, however, "there are no conclusive data to support benzocaine's effectiveness as an anorexiant."

- **Bulk producers** are substances such as methylcellulose (found in Meta-

mucil) that absorb liquid in the stomach, creating a feeling of fullness. The advisory review panel that reviewed OTC weight-control ingredients said that bulk producers are safe but their value in reducing weight has not been established.

Many bulk-producing products, such as methylcellulose, are used primarily as bulk laxatives (a use for which they were found both safe and effective). Some, however, are promoted primarily for weight loss.

One such product is Glucomannan, a chemically processed extract from konjac tubers (a root used as a food in many Oriental countries). According to some of the promotional literature, "Glucomannan absorbs liquid and forms a high-fiber gel that contributes to bulk in your digestive system. Bulk produces a feeling of fullness to help switch off your hunger center...."

FDA is not aware of any bulk-producing product that has been proven to be effective in causing weight loss.

- **Spirulina** is a dark green powder or pill that has been promoted as a weight-loss product. Claims have been made that phenylalanine, an amino acid found in spirulina (and in most other protein sources), "acts on the brain's appetite center to switch off your hunger pangs...."

FDA is not aware of any evidence that phenylalanine is safe and effective as an appetite suppressant.

- **Food supplements** such as bee pollen and certain herbal products (e.g., the Herbalife Slim and Trim Program) are sometimes promoted by manufacturers as effective in causing weight loss. No food supplement is approved by FDA as safe and effective for this purpose.

In her book, *The Carbohydrate Craver's Diet*, Wurtman said, "Serotonin... is made from tryptophan, an amino acid. (Amino acids are the components of protein.) When carbohydrate foods are eaten, insulin is released into the blood. Insulin increases the amount of tryptophan that gets into the brain and subsequently, the level and activity of serotonin. When enough serotonin is produced in the brain, it turns off the hunger for carbohydrates." Wurtman claims that the craving for carbohydrates can be satisfied only by carbohydrate foods because they are the most effective in increasing serotonin in the brain.

More evidence supporting the link between hunger and serotonin and norepinephrine concerns a group of drugs called tricyclic antidepressants, which are used to treat depression. One common side effect of these drugs is increased appetite and overeating, particularly of carbohydrate foods. According to *AMA Drug Evaluations* these drugs work by affecting levels of serotonin and norepinephrine in the brain. Depression—one symptom of which is appetite change and resultant weight gain or loss—is thought to be linked with imbalance of these neurotransmitters, as well as with a third, dopamine.

Dopamine, as well as epinephrine and norepinephrine, are produced by stress—both emotional and physical. They prepare the body for "fight or flight": They stimulate the heartbeat and respiration, inhibit gastric secretions, and stimulate blood glucose.

This is one reason exercise is recommended in weight-loss programs. Exercise, in addition to burning calories, also helps suppress hunger. One theory is that physical activity, which places stress on the body, leads to the release of dopamine, epinephrine, and norepinephrine. NIH's Dr. Skolnick observes that, "It's a pretty common anecdotal observation that if someone runs three miles or plays a pretty vigorous game of tennis, they won't really be in the mood for a big meal

after that, and that feeling persists for a few hours."

But is hunger all in the mind? One substance that seems correlated with fullness is a hormone called cholecystokinin, which is produced in the intestines after eating. A recent study suggests that cholecystokinin may act independently of the hypothalamus to decrease hunger. The study, done in 1981 by researchers at Cornell Medical Center, purported to show that cholecystokinin administered to rats produces satiety by acting on the abdomen, through gastric nerve fibers. Most scientists, however, still believe that cholecystokinin suppresses hunger by acting on the hypothalamus.

Hunger, in fact, does seem to originate predominantly in the mind—which is to say, the brain. The stomach alone apparently has little effect on appetite. Trying to fool the stomach seems to be ineffective in weight control—despite claims for various diet products that bulk in the stomach aids in weight loss.

According to FDA's Advisory Review Panel on OTC Miscellaneous Internal Drug Products, the value of bulk-producing products in reducing weight by controlling appetite has not been established. Most of the products create bulk in the stomach by absorbing up to 50 times their weight in water to form a soft hydrated mass. It has been suggested that this mass creates a feeling of fullness, thus reducing the desire to eat and causing loss of weight.

However, a study reviewed by the panel found that the bulk producer methylcellulose (the active ingredient in some common laxatives) is almost completely gone from the stomach in 30 minutes. The feeling of fullness is thus too short-lived to be very effective.

The comparative fullness or emptiness of the stomach seems to have little effect on whether a person feels hungry. Removing the nerves of the stomach does not in fact suppress appetite. And, say the authors of one physiology text, "Nor does it seem possible on purely theoretical

grounds that a bulk-detecting system could maintain energy balance, since the caloric content of food may bear no relationship to its bulk"—that is, something other than bulk in the stomach must lead to satiety in order to ensure that the proper amount of nutrients are consumed. For instance, a person could fill his stomach with water and still starve.

"Feeding," says Skolnick, "is a very, very complex problem. And the higher you go up the phylogenetic tree [from simple to more complex animal species], the more complicated feeding behavior becomes.... For instance, if you take away the sense of smell from many animals, or humans, feeding behaviors may be dramatically affected." Similarly, altering the ability to taste food can affect the desire to eat. Some studies indicate that rats whose tongues have been anesthetized with tetracaine are less inclined to eat than those who can still taste their food.

Generally, people want to curb their appetites because they're trying to lose weight. But the two are not necessarily correlated because the physiological processes of hunger are not the only factors involved in why people eat. People eat for many reasons—because they're bored, because it's dinner time, because the food is available. The chemical process that takes place in the body is only one stimulus to eat. That's why weight-control specialists frequently advise people trying to lose weight to look at their eating habits instead of taking drugs to alter the body's natural mechanisms.

The appetite, after all, is a marvelous physiological mechanism. It's like an internal mother, making sure you eat enough each day to provide the needed fuel for your body. Although appetite may feel like an inconvenience at times, it's something you can't live without.

Carol Ballentine is a member of FDA's publications staff. Also contributing to this article was Michael L. Herndon, of the publications staff.



What's This Glucomannan?

One of the latest products on the fad diet scene is Glucomannan. According to much of the promotional literature for the product, Glucomannan is "the active fraction of the natural konjac tuber," and one ad boasts that "for over 1,500 years, the Japanese have used this rare fiber to stay slim and lose weight."

There is, in fact, no evidence that Glucomannan causes weight loss, and it is not approved by FDA for such use—or any other use. Neither is it a great Oriental mystery.

The product called Glucomannan is made from the tubers of the plant *Amorphophallus konjac*, also called *Amorphophallus rivieri*, which has been widely cultivated in Japan, China, Indonesia and other countries in East Asia. Its corms (or tubers) are commonly used as food in countries where it is grown. In a 1929 account of Chinese culture, *China—Mother of Gardens*, author Ernest Wilson says, "As an undercrop to maize, *Amorphophallus konjac* is commonly cultivated, the tubers being used as food after their acrid properties have been removed by washing in water. . . . The tubers are ground up with water and made into a curd-like compound."

According to another source, flour from konjac tubers is commonly used in Japanese dishes after being mixed with water to form an edible gel called "Konnyaku." This gel is seasoned and boiled or fried. In Hawaii, the stalks are eaten after being sliced, washed, dried and ground up.

The "Lawrence Review of Natural

Products" (produced by Pharmaceutical Information Associates Ltd.) describes konjac mannan as a polysaccharide (a large molecular weight sugar) derived from konjac flour.

The publication goes on to say that polysaccharides such as guar gum and methylcellulose are useful as laxatives because of their ability to absorb water and swell in the stomach and that "konjac mannan has been reported to alleviate moderate constipation in 1 to 2 days."

This ability to absorb water—and provide a "feeling of fullness" in the stomach—has also led to the claims that the product can promote weight loss. However, there is no evidence that konjac mannan or any other bulk producer is useful for this purpose.

A. konjac is not commonly grown in the United States but can be found sometimes in botanical gardens and some nurseries. Growing four or more feet, it is an impressive sight, with a stalk about two inches in diameter of an olive green color, speckled with rose. It flowers in early spring, bearing a bloom in various shades of red that resembles a huge jack-in-the-pulpit. After the flower dies, the plant produces a wide umbrella-like leaf.

Those who might be tempted to acquire *A. konjac*, either for its edible corms or unusual appearance, should think twice however. Although the flower is a wondrous sight, its smell is extremely noxious, resembling the odor of decomposing animal carcasses. It is not a surprise that the plant is also called Devil's Tongue and Skunk Lily.

Advice On Vaginal Products

Douching will not prevent pregnancy and the labels on vaginal products should carry a warning to that effect, a panel of non-government experts said recently. The panel also recommended a label statement advising pregnant women not to douche, except on the advice and instruction of a physician, because of potential harm to the fetus.

This advice was part of the 58th—and last—panel report in FDA's 10-year-plus review of the safety and effectiveness of the ingredients in and the labeling for all over-the-counter (OTC) drugs. The vaginal drug product report came from the Advisory Review Panel on OTC Contraceptive and Other Vaginal Drug Products, one of 17 panels assisting in the review. The report was published by FDA on Oct. 13, 1983.

The panel evaluated 38 active ingredients marketed for four types of use: relieving minor irritation of the vagina, altering the vaginal acidity to encourage the growth of normal vaginal bacterial flora, producing an astringent effect, and removing vaginal secretions.

Only 7 of the 38 ingredients were safe and effective for their intended use. Povidone-iodine is safe and effective for the relief of minor vaginal irritations, according to the panel. The group also said that calcium and sodium propionate and potassium sorbate are safe and effective for this use. However, in the preamble to the report, FDA said in classifying calcium propionate and sodium propionate as safe and effective the panel relied on studies that were inadequate. Neither ingredient has been previously marketed in OTC vaginal drug products and, therefore, may not be marketed at this time. The agency also noted that potassium sorbate has not been marketed to a material extent in the United States and thus is considered a new drug. It may not be marketed until FDA has approved a New Drug Application for use in vaginal drug products.

Four ingredients were considered

safe and effective for removing vaginal discharge or secretions. The four, all marketed as douches, are dioctyl sodium sulfosuccinate, nonoxynol 9, octoxynol 9, and sodium lauryl sulfate.

Five ingredients for the relief of minor irritation were deemed not safe and effective by the panel. They are hexachlorophene (already banned from vaginal products), phenol, phenolate sodium, sodium salicylate, and sodium salicylic acid phenolate. Such ingredients will have to be taken off the market within 12 months after publication of the final standards for vaginal products.

There were insufficient data to establish the safety or effectiveness of 28 of the ingredients for one or more of the claimed uses. The panel recommended further testing for these ingredients, including a familiar home remedy, acetic acid (vinegar), and a stabilized form of aloe vera, a plant with a centuries-old reputation for healing. (All ingredients with their classifications are listed in the accompanying table.)

In addition to its evaluation of the active ingredients, the panel noted that two inactive ingredients, silica and talc, should not be used in vag-

inal products. Such particulate material is potentially hazardous because it is abrasive and irritating to the tissues, the panel said.

The panel's recommendations for labeling called for including detailed instructions on mixing and using douches. In addition to warnings on use of these products during pregnancy, the labels should advise women not to overfill the vagina with fluid. Doing so can force the fluid into the uterus and cause inflammation.

What should not be included in vaginal product labels are claims such as "effectively cleanses," "routine feminine hygiene," "contains only the mildest ingredients," or "vaginal antiseptic."

Like the 57 panel reports that preceded it, the report of the advisory panel on OTC vaginal products was published in the *Federal Register* by FDA to elicit public comments. After the agency has reviewed the report itself and the comments on it, a monograph or standard will be published setting forth the acceptable ingredients and labeling for this class of drug products.

—Annabel Hecht

OTC Review Milestone

The release of the OTC (over-the-counter) advisory review panel report on vaginal drug products late last year was a milestone for FDA. It marked the end of a major phase of the agency's massive review of the safety and effectiveness of the hundreds of thousands of nonprescription drugs sold in the United States. The review, which generated 58 panel reports, began in 1972.

Although much work remains to be done to convert the panels' recommendations into regulatory action, some consumer benefits have been

realized, in improved products, greater safety, and reduced medical costs.

As instructed by FDA, the 17 panels of non-government experts concentrated on active ingredients that are contained in the 300,000 or so drug products marketed under various names. In all, the panels reviewed more than 700 ingredients, many of them several times because of their various uses in different kinds of products.

The panels found that only about one-third of the ingredients are effective, as well as safe, for their intended uses. The rest require additional proof if manufacturers are to continue to market them, the panels said. This does not mean that only one-third of all OTC drug products



How The Vaginal Product Ingredients Rated

(S = safe and effective; N = not safe and effective; F = evidence of safety and effectiveness insufficient; further testing needed.)

Active Ingredients	Relief of minor irritation	Alters pH	Astringent	Removes vaginal secretions
Acetic acid		F		
Alkyl aryl sulfonate				F
Allantoin	F			
Aloe vera, stabilized	F			
Alum			F	
Benzalkonium chloride	F			
Benzethonium chloride	F			
Benzocaine	F			
Boric acid	F	F	F	F
Boroglycerin	F	F	F	F
Calcium and sodium propionate	S*			
Citric acid		F		
Dioctyl sodium sulfosuccinate				S
Edetate disodium	F			
Edetate sodium	F			
Hexachlorophene	N			
Lactic acid		F		

*FDA disagrees with panel recommendation

contain effective ingredients. Most popular products have safe and effective ingredients even if they sometimes contain other ingredients that are ineffective or have not yet been shown to be effective. For instance, the majority of products for pain and fever contain aspirin or acetaminophen—both safe and effective—whereas questionable ingredients were represented in a small number of products.

The panels not only reviewed the labeling in use but often developed new labeling. For example, one panel recommended putting a sunscreen protection factor (SPF) number on sunscreen product labels to provide consumers information to help prevent sunburn. That suggestion has been widely adopted by the industry.

Based on panel recommendations, FDA has "switched" a number of prescription drugs to OTC status, saving consumers millions of dollars a year. The new OTC drugs include:

- hydrocortisone creams and ointments for topical use
- fluoride rinses and gels for fighting tooth decay
- eight antihistamine or nasal decongestant ingredients for colds and hay fever
- diphenhydramine hydrochloride and diphenhydramine monohydrochloride as nighttime sleep-aid ingredients
- dyclonine hydrochloride as a pain reliever and anesthetic in some rinses, mouthwashes, gargles, sprays and lozenges

(continued next page)

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Some items have been removed from the market as a result of panel recommendations. In 1980, as a result of the review, the agency removed sweet spirits of nitre from the market. The panel concluded that this product, used for many years to reduce fever in children and to treat colic in infants, posed a risk to young children.

In 1982, FDA removed camphorated oil, a liniment, because it was frequently mistaken for castor oil or cod-liver oil, often with toxic results. (See "What Ever Happened To Camphorated Oil?" in the July-August 1983 *FDA Consumer*.)

Other ingredients no longer on the market as a result of the review include:

- hexachlorophene, once common in deodorant soaps but now available by prescription only for special antimicrobial purposes, removed after data showed it could cause damage to the central nervous system
- tribromsalan, an ingredient removed from drugs and cosmetics after it was found to make skin sensitive to light
- zirconium, still safe in most forms of antiperspirants but removed from aerosol products because of concern it could cause lung nodules
- bromides and scopolamine, voluntarily removed from sleep-aids by manufacturers because of safety concerns
- methapyrilene hydrochloride and methapyrilene fumarate, removed from all OTC drug products because these drugs have been demonstrated to cause cancer in animals

FDA also removed from nonprescription sale all daytime sedative products promoted to relieve "simple nervous tension" after the panel reviewing them said people needing tranquilization or sedation during the daytime should see a doctor and not rely on these antihistamine-containing products.

Vaginal Product Rating - Con't.

(S = safe and effective; N = not safe and effective; F = evidence of safety and effectiveness insufficient; further testing needed.)

Active Ingredients	Relief of minor irritation	Alters pH	Astringent	Removes vaginal secretions
Nonoxynol 9	F			S
Octoxynol 9	F			S
Oxyquinoline citrate	F			
Oxyquinoline sulfate	F			
Papain				F
Phenol	N	N	N	N
Phenolate sodium	N			
Potassium sorbate	S*			
Povidone-iodine	S			
Sodium bicarbonate		F		F
Sodium borate	F	F	F	F
Sodium carbonate		F		
Sodium lactate		F		
Sodium lauryl sulfate				S
Sodium perborate	F	F	F	F
Sodium salicylate	N			
Sodium salicylic acid phenolate	N			
Tartaric acid		F		
Vitamin A	F			
Vitamin D	F			
Zinc sulfate			F	

**FDA disagrees with panel recommendation*

Successful Eye Surgery

The May 1983 edition of the *FDA Consumer* featured an article by Wallace F. Janssen, FDA's historian, entitled, "A Beholder Tells of a Lens Implant."...

The May article detailed Mr. Janssen's experiences with a cataract, an abnormality of the eye, eventual corneal surgery, and successful recovery thereafter.... For my family and I, the article was most timely. My mother, at 83 years of age, had a cataract in her right eye. Of more importance was that she had reached that point in the process of the disease where she had to make one of the three choices which Mr. Janssen pointed out and explained so well in his article. Her ophthalmologist, who also is a specialist in cataract and corneal surgery, advised her of the options available and the choice was hers to make.

...despite being keen and well advised by her doctor, she needed help in making her decision. She sought help from my sister and I.... I read her the article, stopping often to answer her questions. Shortly thereafter, following some serious thought, she made the decision to have the

implanted lens. There is no doubt that Mr. Janssen's thoughtful and comprehensive article was the turning or convincing point in helping her make her decision.

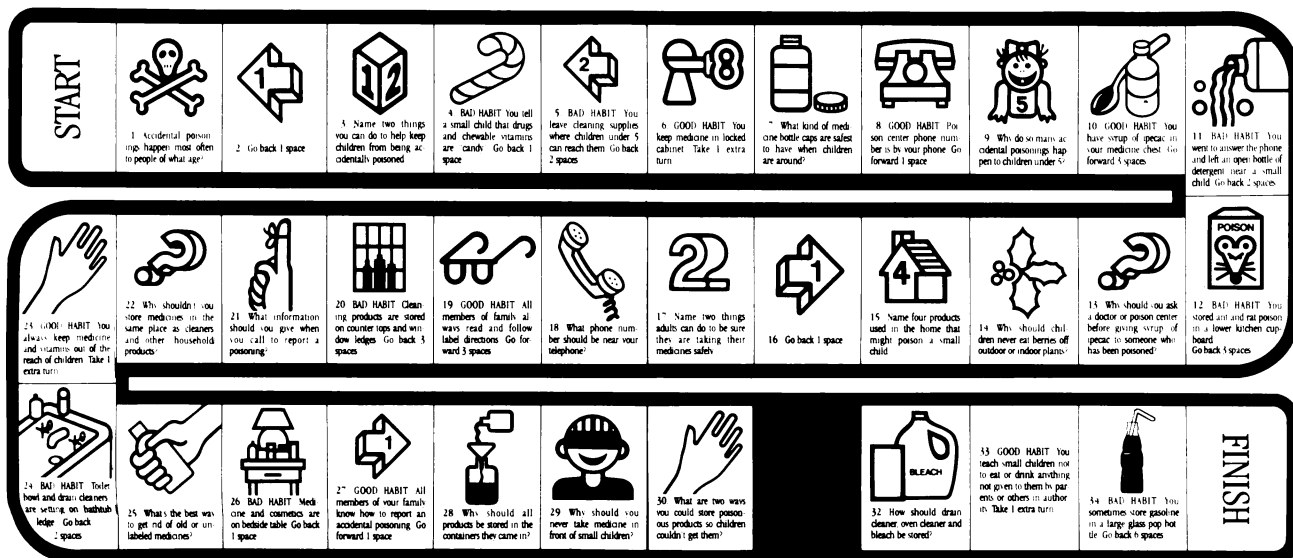
Surgery took place, almost exactly as detailed in the article, on Oct. 5, 1983. On Oct. 17, 1983, an evaluation was made by the ophthalmologist. The report was excellent and my mother was so excited that she wasted no time to call and tell me all about it. She said, "Isn't that just great! Why I can see better than you now. I can get my driver's license back."

David G. Field
FDA program analyst
Boston Region

Sometimes editing a magazine has special rewards.

They Like Safety Game

Thank you for offering such a unique game for children in regards to learning the safety of others with poisonings ("The Poison Safety Game,"



March 1983 *FDA Consumer*.) Girl Scout Troop No. 398 greatly appreciates this learning experience.

Sue Rae Adelman
Sheboygan, Wis.

How Many Died Of Flu

Author Timothy Larkin states in "Flu/Cold—Never The Strain Shall Meet," September 1983 *FDA Consumer*, that "it has been estimated that more than 30 million people died in the United States" during the Spanish flu pandemic of 1918. That would be very nearly one person in three, as the population of the United States in 1918 was just a touch over 100 million. The *Encyclopedia Britannica* (perhaps not the best source for Americana, but authoritative nonetheless) gives the figure as 548,000. I'm inclined to accept that figure....

John T. Pigott
Pebble Beach, Calif.

We goofed. Obviously, the editors weren't as skeptical as several informed readers were of some new figures that were incorporated into the article by mistake while it was under review in FDA. Although the Spanish flu pandemic of 1918-19 took a terrible toll, the loss of human lives was not nearly as great as our figures indicated. Government and other estimates conservatively placed the number of deaths in the United States from flu and pneumonic complications at about 550,000 above the normal 125,000 for the nine-month period that began in September 1918, or a total of 675,000. The worldwide death toll during the pandemic's three waves was estimated to be over 21.6 million, nearly 15.8 million of these in Asia, 2.1 million in Europe, 1.3 million in Africa, 1 million in North America, and less than a million each in Australia-Oceania and South America. However, one demographer estimates that 20 million died in India alone. After 65 years

this pandemic remains one of the worst calamities of modern history.

The Truth About Coumarin

I would like to know the real truth about coumarin. Page 11 of the October *FDA Consumer* states, "There has been no indication that coumarin itself produces this blood-thinning effect in humans," and on page 6 of the same issue is this statement, "Coumarins reduce the ability of the blood to clot." Please clarify this for me.

Gloria Tyndall, R.D.
Spartanburg General Hospital
Spartanburg, S.C. 29303

Although the use of coumarin as food or as a food additive was prohibited by FDA in 1954, this was based not on its blood-thinning properties but on demonstrated liver damage to test animals. Medical literature warns against the ingestion of coumarin and derivatives such as dicumarol when taking certain other drugs, such as aspirin, because of the strong possibility of a drug interaction causing internal bleeding.

FDA knows of no testing of coumarin in humans, and therefore cannot say for sure that coumarin in food products will act as an anti-coagulant, but the chemical similarity between coumarin and its derivatives used as anticoagulant drugs is close enough for concern about a potential for adverse effects. The case study describing excessive menstrual bleeding in a young woman who had been drinking large quantities of herbal teas containing coumarin is obviously relevant enough to suggest caution in using coumarin in an herbal tea, in a flavoring extract, or ingesting in other ways. This makes good sense, even if there were no proof whether the menstrual bleeding could have been caused by other substances the woman may have ingested, or interaction of such substances with the coumarin.

There are several derivatives of coumarin used as drugs. Warfarin, for example, used as a blood-

thinning medication, is a synthetic closely related to coumarin.

More On 'Melencolia I'

The reproduction of the engraving by Albrecht Durer that has come to be known as "Melencolia I" for the article "Melancholy and the Muse" in *FDA Consumer* for October 1983 is appropriate, but the surmise quoted from Panofsky that it was occasioned by the artist's sorrow at the death of his mother is simply a guess. It misses the point of the picture entirely.

The star rising in the east is Sirius, the brightest star in Canis Major, the constellation of the dog. This is further exemplified by the dog behind the banner with the name and the dog sleeping in the



foreground. The period of the year must then be July, August and early September, since the artist is working in the north temperate latitudes when Canis rises with the sun. These days have been known traditionally as "the dog days," a time when dogs are supposed to be subject to madness and people are supposed to become listless, depressed and melancholic.

Durer had studied mathematics with Pacioli in Venice in 1494 and 1505. He drew the first printed star maps in 1515, numbering the stars on the charts according to Ptolemy's list. He was attempting to do for the artist what Ptolemy had done for the astronomer, to make a mathematical science of painting. In his engraving he shows Urania, the muse of astronomy, who is identified by the compass she holds and the globe at her feet. The odd-looking solid behind the dog is an acute rhombohedron, one of many such that Durer had worked with. The ladder against the building, the scattered carpenter's tools, pieces of wood, and lead being melted indicate that construction is under way, but in abeyance, perhaps because the mood of the muse, and also the artist, is more contemplative than constructive. Even great minds can become depressed when they reflect on the tasks ahead to convey their meaning and intent to others.

Allan J. Ryan, M.D.
Editor-in-Chief
Sportsmedicine Magazine

As noted in the caption accompanying the engraving, FDA Consumer's source of information on the engraving was E. Panofsky's book Albrecht Durer, Vol. I, printed by Princeton University Press in 1943. However, we would have liked to have had Dr. Ryan's analysis before we printed the October issue.

Of Pills That Pack Too Much Punch

by Evelyn Zamula

*Eye of newt, and toe of frog
Wool of bat, and tongue of dog
—from Shakespeare's Macbeth*

How do tiger bone, rhinoceros horn, turtle shell, male mouse droppings and scorpions sound for treating your ailments? Or a pill that contains about 23 different herbs, a potent prescription drug or two, and perhaps a dash of lead and cadmium?

These are some of the ingredients that have turned up in so-called Chinese herbal remedies, peddled to arthritis sufferers all over the United States under a dozen names. These pearl-sized, black or brown pills almost always promise the buyer long life and freedom from pain. Sometimes, though, they end up delivering

serious illness or death.

Herbal remedies from the Orient are nothing new. They've been coming into the country for over a century from Taiwan, Hong Kong and Singapore. For most of that time users of the remedies haven't reported any particularly harmful effects to health authorities. However, experience with the pills has taken a more sinister turn in the past 10 years or so. Some people have died from the pills; many cases of illness have been reported to FDA.

What has changed? In a 1975 article in the *Journal of the American Medical Association*, two University of California physicians speculate that manufacturers of the Chinese herbal remedies, hoping to cash in on the popularity in this country of health foods and "organic medicines," have put a little something extra in their pills. Potent anti-inflammatory and analgesic drugs have been added, probably to insure improvement of painful symptoms and to attract repeat customers.

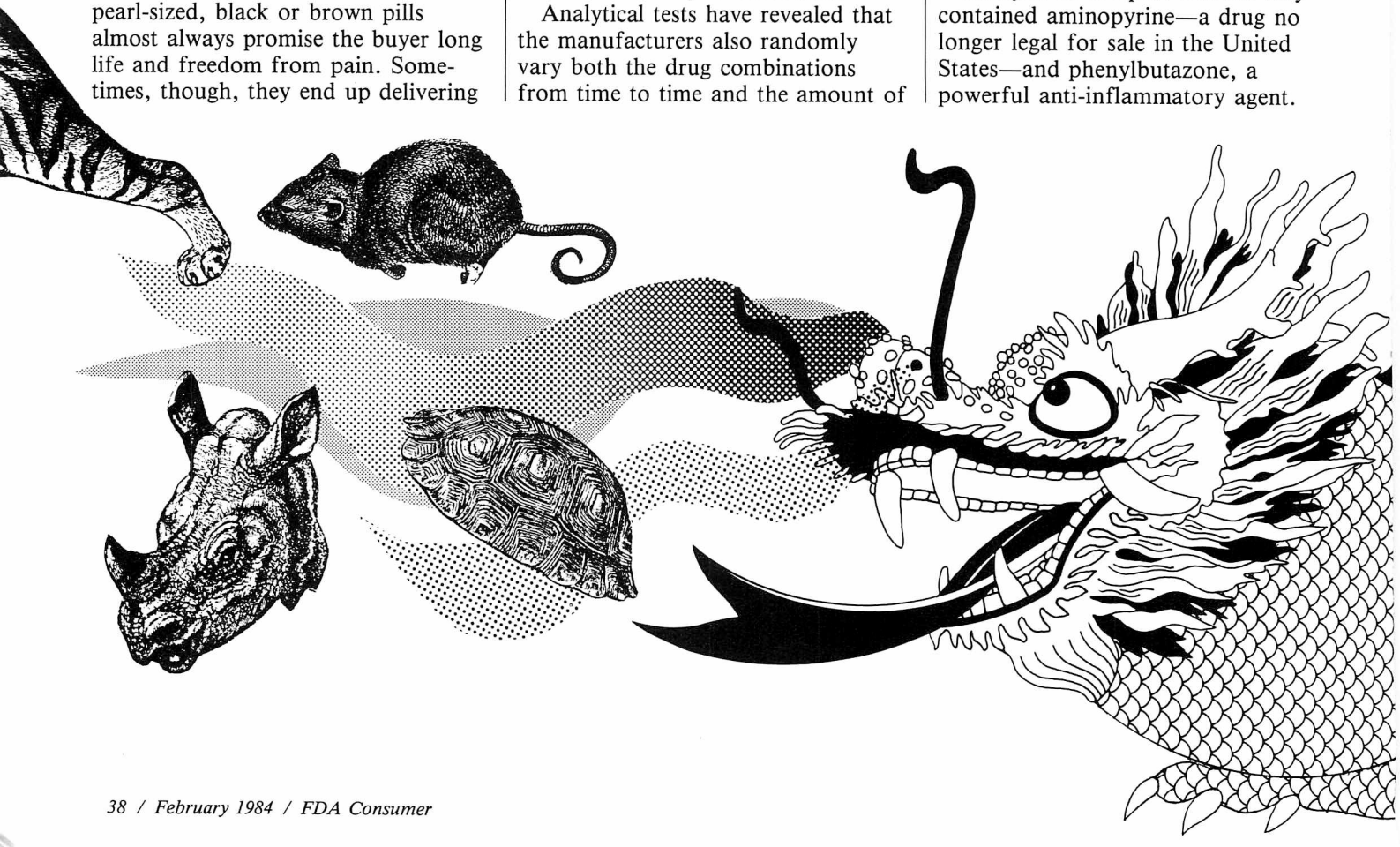
Analytical tests have revealed that the manufacturers also randomly vary both the drug combinations from time to time and the amount of

each drug, depending probably on the availability of the individual drug components. Or maybe they figure if they include a variety of drugs in the pills, they are bound to relieve *something*.

Sometimes they do, and that's unfortunate. Some who use them feel better, have less pain, less discomfort. The danger is that many patients may already be taking drugs prescribed by a physician, and the drugs in the herbal remedies may interact with the other medications, or cause serious side effects, often with tragic results.

In 1974 in the San Francisco Bay area three cases of serious illness and one death were reported from agranulocytosis—a sudden drop in the production of certain white blood cells that leaves the body defenseless against bacterial invasion. The patients had been taking 8 to 12 Chinese herbal pills daily for weeks or months to relieve arthritis or back pain.

Analysis of the pills showed they contained aminopyrine—a drug no longer legal for sale in the United States—and phenylbutazone, a powerful anti-inflammatory agent.



The Arthritis Foundation reports that other herbal remedies from the Orient analyzed at the same time were found to contain steroids, minor tranquilizers and common painkillers. Nowhere on the packages or the inserts were these drugs mentioned—only herbal substances.

In 1980 FDA received reports of a death, in Atlanta, of a rheumatoid arthritis victim who had been taking "Chufong Toukuwan" pills containing indomethacin, an anti-inflammatory drug. Also reported from New York was the serious illness of a man who took pills containing hydrochlorothiazide, a diuretic.

FDA has warned the public and health officials on a number of occasions about the Chinese herbal remedies. The agency has asked the U.S. Customs and Postal Services to detain the pills if they come into the country—but these products are hard to keep out.

They enter the United States in the baggage of or on the persons of travelers. They are mailed in small shipments from the Far East to health food stores, Oriental goods stores, novelty shops, and even directly to the consumer. Or they may be smuggled in from Mexico or Canada.

A typical shipment of this kind contains 60 pills and is packaged in a cellophane bag or glass bottle. It may be enclosed in a brightly colored cardboard box. Depictions of men and women suffering from back or leg pains may appear on the package.

Labeling may be in English and suggest that the pills are good for arthritis, osteoarthritis, rheumatism, bone pain, neuralgia or similar conditions. Or there may be no labeling at all. The pills sell in the neighborhood of \$55 to \$60 per hundred. When pills are detained and shipped back to the distributor, the customer may lose money but still benefit by avoiding the peril of the pills themselves.

One of the larger distributors of these pills on the East Coast was identified through a chain of events played out on the West Coast. A concerned citizen complained to the Oregon State Board of Pharmacy that a little gift shop in Tillamook, Ore., was selling pills for arthritis. The Tillamook police collected some of the pills and submitted them to the state pharmacy board, which turned them over to FDA's Seattle district laboratory for analysis. When the lab report revealed that they contained phenylbutazone, the police seized the remainder of the shop's stock of pills. The gift shop owner told officials his supplier was the Jen Tai Co. in Portland, Ore.

FDA investigators called on the Portland company, a tiny Oriental apothecary shop, a place fragrant throughout from herbs in jars that lined the walls of the shop. Customers, Asians and non-Asians alike, would bring in slips of paper—given to them by acupuncturists or "health counselors." The papers contained the names of various herbs. The staff would blend an

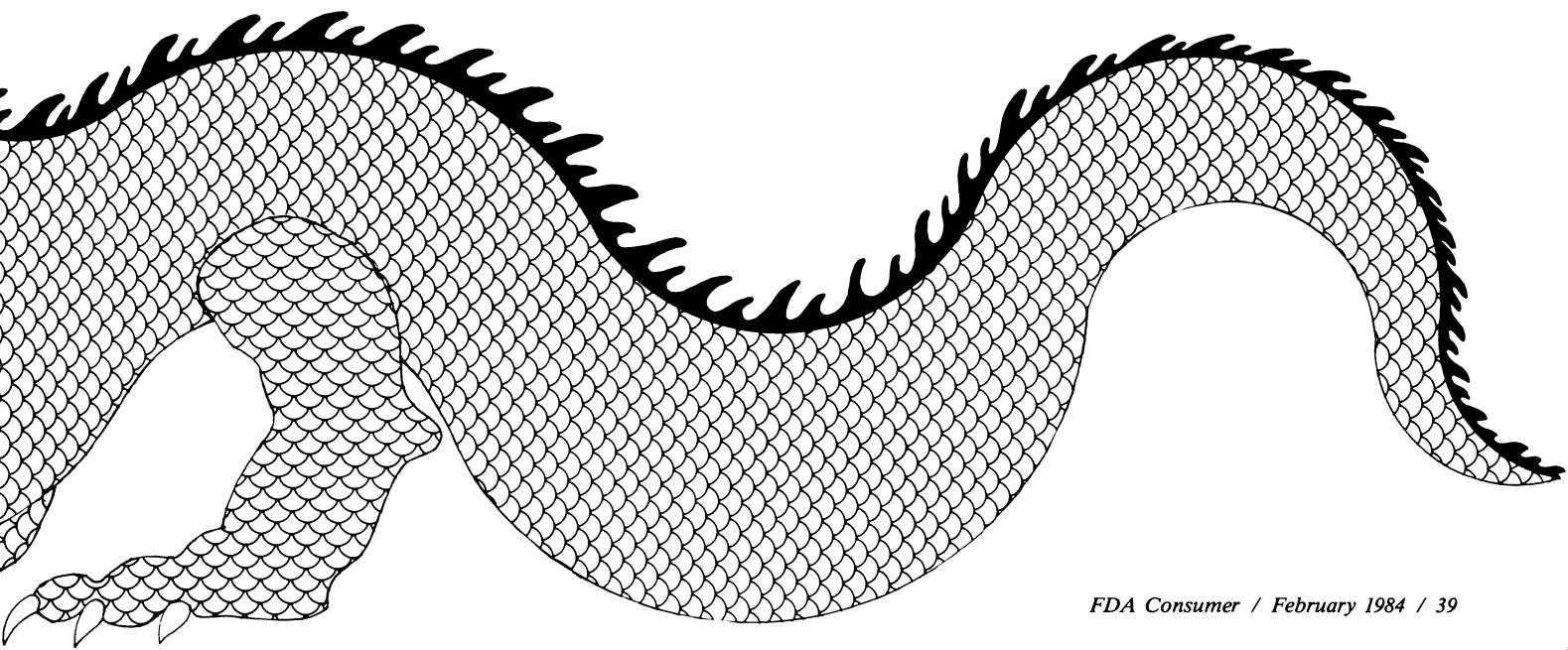
herb mixture as directed on the slips of paper.

But the shop had other things for sale, specifically certain medications called Tai Fung arthritis pills, the same pills that had turned up in Tillamook. When FDA warned the owner, Jen Tai Tsui, both verbally and in writing that the pills were unapproved new drugs, he agreed to stop distributing them and promised to destroy all that he had left.

Just to make sure he had done so, a Seattle investigator then ordered a supply by mail. He received the pills, and they were accompanied by an information sheet that recommended a dose starting at 12 pills a day and decreasing gradually to six to eight pills daily. An analysis by the Seattle district lab showed that each pill contained 16 to 17 milligrams of phenylbutazone. Taken as directed, the pills would have presented a health threat and could have been fatal.

FDA asked the court for an injunction against the Jen Tai Co. and its owner, charging sale of prescription drugs without a valid prescription, misbranding through illegal labeling, and other violations of the Food, Drug and Cosmetic Act.

Jen Tai Tsui signed a consent decree of permanent injunction, agreeing to stop selling the drugs. He also was required to post a notice in a conspicuous place in his shop warning customers that the pills contained phenylbutazone and could be dangerous, and was required to so



advise his mail-order customers. He asked all his customers to return whatever pills they had for destruction under FDA supervision.

Tsui told FDA he had bought the pills from an Oregon travel agent, who in turn implicated the New World Trading and Travel Co. in Philadelphia.

In May 1983 a U.S. customs agent assigned to the case spotted and recognized the proprietor of New World Trading and Travel Co. as the same man who just the month before had made a false declaration of goods from the Orient. What he had declared as teas and spices was in fact powdered rhinoceros horn, much prized by certain Asians for restoring sexual vigor. Trading in rhino horn is

prohibited by the Endangered Species Act. The rhino powder was denied admission into the country.

After that episode, FDA and the Customs Service focused more attention on the little travel agency. Customs sent two young women agents to the shop, and they encountered no trouble buying both rhino horn powder and a Chinese herbal medicine (Chuifong Toukuwan). Based on the undercover buys, along with the previous fraud, smuggling and violations of Endangered Species Act, Customs obtained a warrant to search the premises of the New World Trading and Travel Co.

On Aug. 5, 1983, a U.S. customs search team and two FDA investigators entered the travel agency. The

search revealed the firm to be a large smuggling, repacking and distribution center for Chinese herbal medicines. Placed under seizure were 6,055 boxes of Chuifong Toukuwan, 905 boxes of rhino horn powder, 275 boxes of miscellaneous Chinese medicines, and 19 boxes of U.S.-manufactured prescription antibiotics that were being held for sale without prescriptions. The total value was \$91,958.

U.S. Customs is continuing its investigation, an investigation that may save some unsuspecting folks from wasting money on dangerous and unproven Chinese witches' brew.

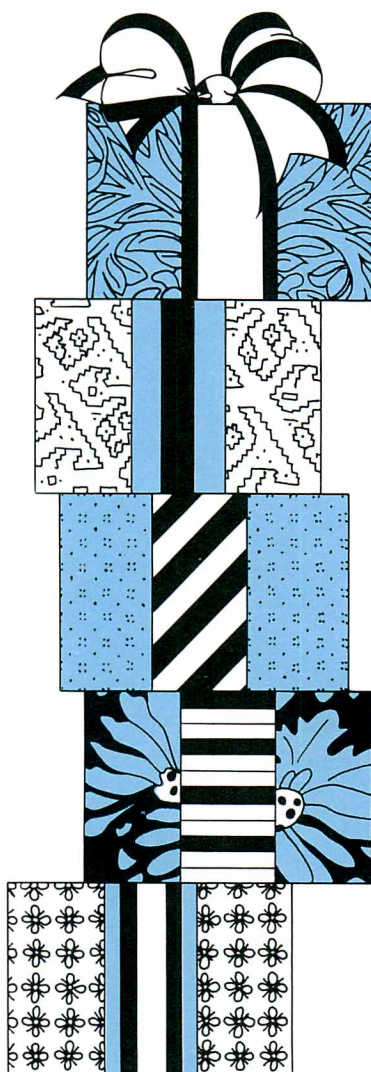
Evelyn Zamula is a member of FDA's publications staff.

Quacks Used Smuggling

To smuggle means to import or export anything without paying lawful customs charges or duties. And it was because of a smuggled package that FDA's **Dallas district** office first learned about the illegal activities of Arthur and Lucille Usner.

A year or so ago Mr. Usner was stopped at the U.S.-Mexican border by a U.S. customs official who was interested in a package Usner didn't bother to declare. Because it contained a drug, Customs notified FDA. In a follow-up investigation, Dallas district officials learned that the Usners were using their home in Albuquerque, N.M., to run a business called Metabolic Products.

Later a physician called FDA's at-



tention to a Metabolic Products ad offering a variety of unfamiliar drug products for sale to cure an unusual list of human ailments. The Dallas district's medical officer made an undercover buy and received not only the drugs he ordered but booklets describing the Usners' products and the many conditions they claimed could be treated. The Usners specialized in alternative cancer treatments, all consisting of unapproved new drugs. The booklets were subsequently used as evidence of unapproved labeling.

Investigation of the Usners' home business revealed a storehouse of illegal drugs, most smuggled into the United States from Germany disguised as gifts. U.S. customs officials seized approximately \$15,000 worth

of the smuggled drugs still in their shipping packages. At FDA's request the New Mexico Board of Pharmacy embargoed the remaining drugs until an injunction was filed on Aug. 17, 1983.

When FDA investigators sorted out the embargoed stocks, they found an astonishing number and variety of drugs, including injectable products made from parts of animals to cure ailments of the corresponding parts of humans, tablets and injectable forms of Laetrile, KH3 (a version of the so-called rejuvenating drug Gerovital), and even DMSO. The embargoed stock, worth approximately \$8,000, was destroyed in a landfill under the supervision of FDA and the New Mexico Board of Pharmacy.

As a result of these actions, the Usners entered into a consent decree that permanently enjoins them from any activity involving any article regulated by FDA unless such activity is reviewed and approved by the agency. It was estimated that the Usners' business in illegal and/or smuggled drugs totaled more than \$500,000 over a two-year period.

Second Look

People who have a fear of flying might be too nervous to eat and thus wouldn't worry about the safety of the food served aboard an airliner, but most airline travelers take it for granted that whatever is offered will be safe and wholesome.

FDA investigators routinely inspect food and drink, including drinking water, served on airliners and on other conveyances that travel in interstate commerce—ships, buses and trains.

Because caterers generally prepare food served on airliners, FDA investigators inspect catering facilities to make certain the food is prepared properly. FDA classifies the facilities as "approved," "provisionally approved," or "not approved." Conveyances are not permitted to deal with caterers that are classified as "not approved."

Ogden Food Service Corp. is one of the catering businesses serving airlines out of New York's JFK International Airport, one of the busiest in the world. FDA's **Brooklyn**



district office is responsible for inspecting the caterers serving this airport as well as the smaller, but also extremely busy, LaGuardia Airport. An estimated 50,000 meals per day are produced by the caterers serving these airports.

In July 1983 district investigators made a routine inspection of Ogden's

facilities at the airport and found several objectionable conditions and practices, the most serious being improper storage of food and the use of unclean equipment. Based on this inspection, the firm was classified as "provisionally approved."

This meant that all carriers being catered by Ogden were required to be

notified of FDA's findings, and significant improvements had to be made within 30 days or the classification would be changed to "not approved." The firm improved on its conditions and practices, and the classification was changed to "approved" following a reinspection by the Brooklyn FDA office.

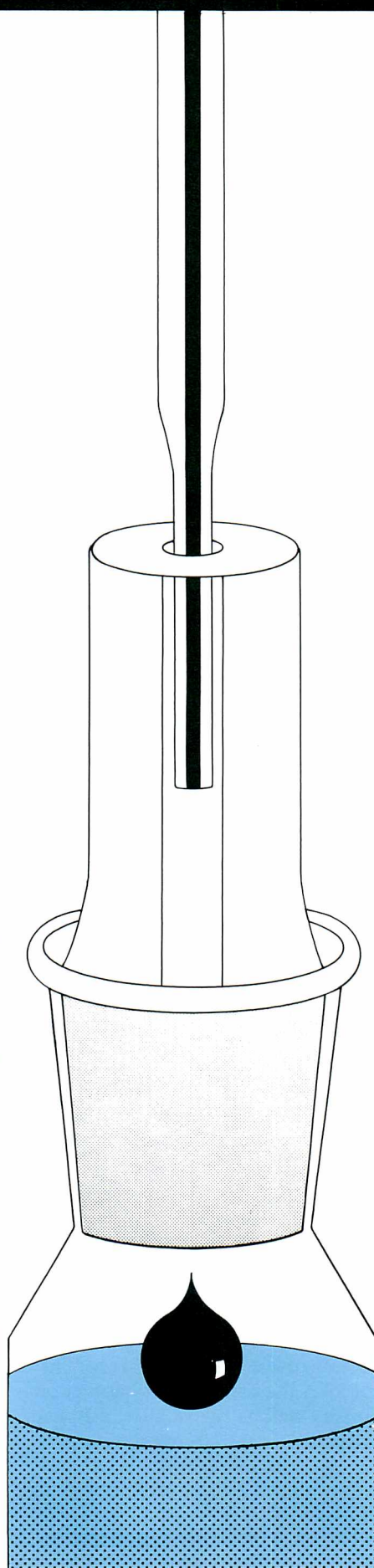
Blood Test

Investigators from FDA's **Boston district** found double trouble when they checked a report of inaccuracy of a medical device made by Copley Pharmaceuticals Inc., Boston.

The first problem was with the device itself—a copper sulfate solution commonly used to test the hemoglobin content of potential blood donors. In the test a sample of the potential blood donor's blood is dropped into the copper sulfate solution. Protein in the blood reacts with the solution to form a sac of copper proteinate, which encases the sample. If the blood has a satisfactory, or healthy, level of hemoglobin, the sac will sink to the bottom of the solution. But if the blood is deficient in hemoglobin—if the person has anemia, for instance—the sac will remain suspended for 15 or more seconds before sinking or will float to the surface.

The labels on bottles of copper sulfate list the product's specific gravity, which affects the sac's tendency to sink or float. For correct test results, this labeled figure must be accurate. In the case of Copley Pharmaceuticals' products, it was not.

A nurse from a California blood bank had reported to FDA that a quality control analysis done by the



blood bank found that the specific gravity of the product was less than indicated on the label. FDA's ensuing inspection determined that the company was aware of the problem and attributed it to inaccuracies in one of its pyknometers, an instrument used to measure specific gravity. Evidently the cap on the pyknometer had been replaced by a cap from a different model, altering the weight of the device.

The firm said it had repaired the pyknometer and had advised consignees to destroy the defective product. However, when investigators made a verification check of company files, they found a second problem: There were serious deficiencies in the company's procedures for recording complaints and conducting recalls.

For instance, the company had no record of the complaint that led to the FDA inspection. There was no documentation of the firm's claimed attempts to recall the defective product, such as copies of letters or records of phone calls. And although company officials said 600 cases of the copper sulfate solution had been destroyed, they did not remember the name of the company that did the work and had no proof of payment for such services.

The district accordingly requested that the firm formally recall all lots of the product that might be defective, this time with appropriate documentation and under FDA supervision.

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

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.

■ The isotope **Californium-252** has FDA's approval for use as a sealed neutron source for the measurement of moisture in the inspection of raw and packaged food, and in controlling food processing (FR Oct. 11, 1983).

■ FDA's Office of **Orphan Products Development** is looking for a sponsor to submit a new drug application for a compound including citric acid, gluconic acid and magnesium hydroxycarbonate to dissolve urinary tract calculi and to prevent encrusting of indwelling urinary tract catheters (FR Nov. 10, 1983).

■ The Treasury Department's Bureau of Alcohol, Tobacco and Firearms has issued a final rule rescinding **ingredient labeling regulations for alcoholic beverages**. Mandatory label disclosure of FD&C Yellow No. 5 is still required to alert those people who are allergic to this dye (FR Oct. 6, 1983).

■ Drugs that are switched from prescription to nonprescription status need a new **National Drug Code (NDC)** number. NDC is FDA's system for identifying drug products. The agency said the marketing of an OTC drug with the same NDC number that it had as a prescription drug slows the processing of health insurance reimbursement claims (FR Nov. 30, 1983).

■ Corn containing between 20 and 100 parts per billion **aflatoxin** can be shipped interstate if state officials assure FDA the corn will be fed only to mature beef cattle, swine and poultry and will not be used for dairy or immature animals or in corn products for human consumption. Drought and high humidity in 1983 contributed to the development of aflatoxin, a potentially harmful toxin

caused by mold. The policy will remain in effect until January 1985 (FR Nov. 25, 1983).

■ The Public Citizen Health Research Group has petitioned FDA to include a **pregnancy-nursing warning** on all over-the-counter (OTC) drugs regardless of how they are used. Labels of OTC drugs intended for systemic absorption (i.e., taken orally) must include the warning: "As with any drug, if you are pregnant or nursing a baby seek professional advice before using this product." Drugs used topically (on the skin) and mouthwashes regulated as drugs are not covered by this regulation (FR Nov. 30, 1983).

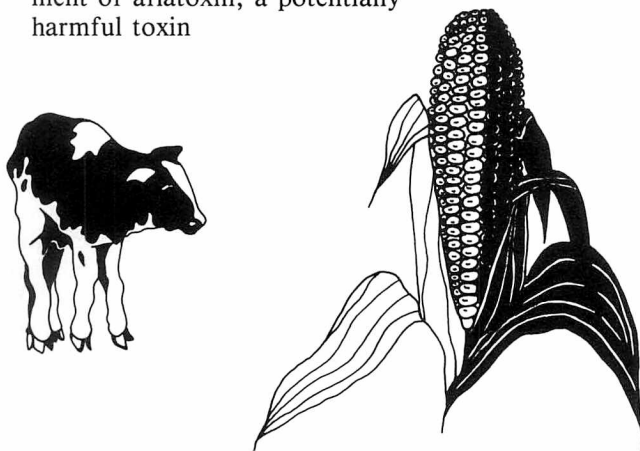
■ FDA is proposing to amend the performance standard for **laser products** to, among other things, extend the applicable wavelength range, simplify and clarify certain definitions, and modify requirements for safety interlocks (FR Nov. 30, 1983).

■ **MARKET BASKET:** FDA has proposed revoking GMP (good manufacturing practice) regulations for **smoked and smoke-flavored fish**. The regulations have not been enforced since a 1977 ruling by the U.S. Court of Appeals for the Second Circuit held that the smoked whtiefish regulation was promulgated in an arbitrary manner and was invalid. . . . Also proposed are amendments to FDA's **standards of identity** for canned bean sprouts, lima beans, carrots, green sweet peppers, red sweet peppers, and potatoes to permit the use of calcium salts as firming, or crisping, agents (FR Oct. 21, 1983).

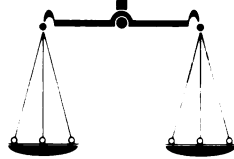
Interested persons have been asked to review the international standards for **quick-frozen fillets** of cod and haddock, ocean perch and flat fish and to comment on the need for similar U.S. standards (FR Nov. 15, 28 and 30, 1983).

July 1, 1985, is the effective date for FDA's new regulation permitting the use of **antimycotics** on the surface of bulk forms of a variety of cheeses, including Asiago, Caciocavallo Siciliano, mozzarella, and provolone (FR Oct. 24, 1983).

Four issues relating to the standard of identity for **baked products** have been resolved following a formal evidentiary public hearing: Lecithin will be permitted as an optional ingredient in egg bread as well as in other bakery products; spices, spice oil, and spice extract may be used even though they impart an egg-like color; artificial coloring as an optional ingredient in standardized bakery products is permissible; and the standard of identity for the various types of egg breads requires a minimum content of the whole egg solids of one medium-sized egg per pound (FR Nov. 9, 1983).



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 Food and Drug Division, Office of the General Counsel, HHS.

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

SEIZURE ACTIONS

Foods/Poisonous and Deleterious Substances

PRODUCT: **Swordfish, frozen**, at Rochester, W. Dist. N.Y.; Civil No. 82-1020-T.

CHARGED 11-3-82: When shipped by Crocker & Winsor Seafoods, Boston, Mass., the article contained the added poisonous and deleterious substance mercury, which might render it injurious to health—402(a)(1).

DISPOSITION: Default—ordered destruction. (F.D.C. No. 63875; S. No. 82-252-486; S.J. No. 1)

Foods/Contamination, Spoilage, Insanitary Handling

PRODUCT: **Basil, and anise seed**, at Brooklyn, E. Dist. N.Y.; Civil No. 79-C-814.

CHARGED 3-28-79: While held by Gel Spice Co., Inc., Brooklyn, N.Y., the articles contained rodent filth and had been held under insanitary conditions—402(a)(3), 402(a)(4). **DISPOSITION:** Consent—authorized release to the dealer for salvaging. After some delay, the dealer changed plans and destroyed the articles. (F.D.C. No. 62218; S. No. 79-184-894; S.J. No. 2)

PRODUCT: **Pinto beans (two lots)**, at Yakima, E. Dist. Wash.; Civil No. C-82-335-RJM.

CHARGED 4-30-82: While held by Northwest Produce Co. Inc., Yakima, Wash., one lot of the pinto beans contained

rodent filth, and both lots had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 63711; S. No. 82-279-447; S.J. No. 3)

PRODUCT: **Tomatoes, peeled, canned**, at Miami, S. Dist. Fla.; Civil No. 83-0390-Civ-EBD.

CHARGED 2-16-83: While held for sale, the article was contained in swollen, rusty and/or leaking cans—402(a)(3).

DISPOSITION: Default—ordered destruction. (F.D.C. No. 63966; S. No. 83-268-780; S.J. No. 4)

Drugs/Human Use

PRODUCT: **Phendimetrazine tartrate tablets and capsules**, at Louisville, W. Dist. Ky.; Civil No. C78-0358-L(A).

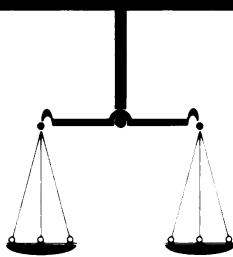
CHARGED 9-6-78: When shipped by various manufacturers, the articles—labeled in part “QC Timely Appease Tablets . . . Distributed by Queen City Pharmacal Co., Cincinnati, Ohio,” “Phendimetrazine Tartrate tablets 70 mg speckled Barr Laboratories, Inc., Northvale, N.J.,” “Obepar TD . . . Capsules Manufactured for Parmed Pharmaceuticals, Inc., Niagara Falls, N.Y.,” “Tutag . . . Detroit, Michigan [or ‘Broomfield, Colorado’] . . . Granucaps,” and “Phenazine Timecaps . . . Anorexiant . . . Mfg. For: M.M. Mast & Company Cleveland, Ohio”—were new drugs without effective approved New Drug Applications—505(a).

DISPOSITION: Default—ordered destruction. (F.D.C. No. 61849; S. No. 78-132-602 et al.; S.J. No. 5)

Medical Devices

PRODUCT: **Muscle stimulators, electrical, Bio-Tone**, at Sandy Springs, N. Dist. Ga.; Civil No. C81-75A.

CHARGED 1-13-81: The articles, which had been distributed by Bio-Body Centers of America, Inc., New York, N.Y., were accompanied by a brochure (labeled in part “Bio-Trim Slimming Center . . . Lose Inches Lying Down”) and charts (labeled in part “Muscle Group . . . Abdominal Muscle . . . Heavy Hips and Legs”), which labeling contained false and misleading claims for having dramatic inch reduction, contributing to fat loss by general improvement in “the muscle tones in your body,” creating a feeling of health and well-being, and being particularly good for flab over the “iliac chest”—502(a); the articles’ labeling lacked adequate direc-



tions for use for their intended purposes (weight reduction and slimming) and were not exempted—502(f)(1); and the articles' labeling lacked adequate warnings against unsafe uses—502(f)(2).

DISPOSITION: The articles were claimed by Vernon Brabham Jr., Sandy Springs, Ga., and Medequip Investment Corp., Columbus, Ga. A consent decree of condemnation (entered into by the claimants in the interests of resolving the controversy and without admitting to knowledge of the alleged violations prior to the date the complaint was filed) authorized release of the articles for bringing into compliance, by relabeling the devices with revised labeling and with the prescription device legend. The decree prohibited the claimants as follows: from claiming effectiveness for the purposes charged in the complaint; from claiming that such articles might be used without the prescription of a licensed practitioner; from using the articles outside a valid doctor/patient relationship; and from using the articles in their "Bio-Trim Slimming Center" establishment.

However, the articles were not relabeled. The claimants moved for reconsideration of the consent decree of condemnation, and moved for leave to amend their claim and to assert a defense and counterclaim against the government. The government asserted that the claimants had failed to comply with the terms of the consent decree and moved for a default decree ordering the articles destroyed. The government also opposed the claimants' motions. On Dec. 21, 1982, the court found for the government. The court found the following: that the claimants were not able to meet the burden of showing either newly discovered evidence or a change in circumstances that worked a grievous wrong; that the amendments sought by the claimant would be subject to dismissal and were therefore futile; and that, since the claimants showed no willingness to comply with the terms of the consent decree, the articles should be destroyed. (F.D.C. No. 63169; S. No. 80-164-287; S.J. No. 6)

CRIMINAL ACTIONS

DEFENDANTS: **J.H. Haar & Sons**, and **George A. Haar**, president, North Bergen, Dist. N.J.; Cr. No. 81-6139G-01. **CHARGED** 9-16-81: Rice (count 1) and pancake flour mix (count 2) were held under insanitary conditions and were contaminated with rodent filth—402(a)(3), 402(a)(4). **DISPOSITION:** Guilty plea by corporation to both counts;

\$10,000 fine on count 1, \$10,000 fine on count 2 suspended, and probation for three years. Guilty plea by individual; imprisonment for six months suspended, and probation for two years, with a special condition of probation being payment of \$1,000 fine. (F.D.C. No. 63188; S. No. 80-209-462; S.J. No. 7)

DEFENDANTS: **International Baking Co., Inc.**, **Simon Mani**, president, **Jack Khashou**, vice president, and **Hatem Safar**, plant manager, Arlington, N. Dist. Texas; Cr. No. 4-82-114.

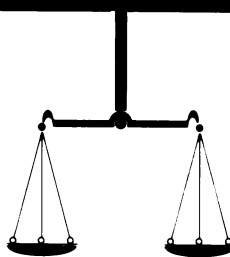
CHARGED 10-19-82: One lot of hulled sesame seeds (count 1) and two lots of whole wheat flour (counts 2 and 3) were held under insanitary conditions in a building accessible to insects and were contaminated with insect filth—402(a)(3), 402(a)(4); and, when shipped to Shreveport, La., whole wheat bread (count 4), labeled in part "Mr. Pita Whole Wheat Bread . . . International Baking Co., Inc. General Office . . . Vernon, Calif.," had been prepared and packed under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: The corporation pleaded guilty to count 1 and was fined \$1,000. Simon Mani pleaded guilty to counts 1, 2 and 3 and was fined \$1,500. Jack Khashou pleaded guilty to counts 1 and 4 and was fined \$1,000 and sentenced to imprisonment for one year; the imprisonment was suspended and probation imposed for two years. Hatem Safar pleaded guilty to count 1 and was sentenced to imprisonment for six months; the imprisonment was suspended and probation imposed for one year. (F.D.C. No. 63627; S. No. 81-210-574 et al.; S.J. No. 8)

DEFENDANTS: **Pittston Warehouse Corp.**, and **Robert F. Chiarello**, president, Brooklyn, E. Dist. N.Y.; Cr. No. 80-00-315.

CHARGED 7-1-80: Sage leaves, mustard seed, marjoram, poppy seed, chilies, pimento, basil leaves, ginger, and cassia from Indonesia, China, Seychelles and Madagascar were held under insanitary conditions in a manner accessible to rodents and insects and were contaminated with rodent and/or insect filth—402(a)(3), 402(a)(4).

DISPOSITION: The defendants served a demand for a bill of particulars, a notice of motion for discovery and inspection, and a notice of motion to suppress inspectional evidence. Subsequently, a consent decree of permanent injunction was entered into and the criminal action was **dismissed**. (F.D.C.



No. 62093; S. No. 78-140-783; S.J. No. 9)

INJUNCTION ACTIONS

DEFENDANTS: **Alva Vet Supply Co., Donald E. Petermann**, partner, and **Michael B. Stevens**, partner, Alva, W. Dist. Okla.; Civil No. 82-2048-R.

CHARGED 11-10-82 in a complaint for injunction: That veterinary prescription drugs, including chloramphenicol, dexamethasone and isoflupredone acetate, were held for sale, offered for sale, and sold to unauthorized persons without a prescription or other order of a licensed veterinarian; that, accordingly, as prescription veterinary drugs, their labeling lacked adequate directions for lay use and were not exempted from such requirement because the drugs were not being sold only to or on the prescription or order of a licensed veterinarian and were not in the possession of a licensed veterinarian for his professional use; that, despite warnings, the defendants continued to violate the law; that an FDA inspection revealed drug storage and record-keeping deficiencies, including a lack of filed prescriptions and the storage of prescription drugs on retail shelves in easy reach of any lay person entering the store—502(f)(1).

DISPOSITION: A consent decree of permanent injunction enjoined the complained of violation and enjoined the sale of any prescription veterinary drug unless and until: procedures were established so all such prescription drugs were stored in an area accessible only to firm employees; procedures were established so such prescription drugs were sold only to or on the prescription of a licensed veterinarian; records were established and maintained demonstrating that every such sale was properly based; an accurate drug inventory was prepared and maintained; and the defendants reported to FDA on the measures that they had taken to assure compliance. (Inj. No. 1014; S. No. 82-267-541 et al.; S.J. No. 10)

DEFENDANTS: **Fry Krisp Food Products, Inc., Richard G. Neuenfeldt**, president and treasurer, and **Richard J. Neuenfeldt**, vice president and plant manager, Jackson, E. Dist. Mich.; Civil No. 82-60417.

CHARGED 12-13-82 in a complaint for injunction: That the defendants, at their Jackson, Mich., plant manufactured, processed, packed, labeled, held and distributed in interstate commerce dry breeding and batter mixes that had been prepared,

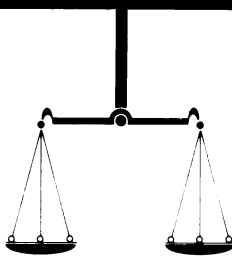
packed and held under insanitary conditions; that the defendants, at their Jackson, Mich., plant, had also manufactured, processed, packed and labeled such foods, which were held for sale after interstate shipment of their components; that FDA inspections of the defendants' plant had disclosed a number of specified insanitary conditions; and that the defendants had been repeatedly warned of the insanitary conditions and practices in their plant—402(a)(4).

DISPOSITION: The defendants moved to seal the court file, and to suppress access to the file except to those involved in the litigation. The government opposed such motion to suppress, arguing that the disclosure of the FDA investigative reports (the basis for the action) was mandated by statute, and that to grant the motion to suppress would be, in effect, enjoining the operation of FDA regulations relating to the public disclosure of information. The court ruled in favor of the government. Subsequently, the parties entered into a consent decree of permanent injunction.

The consent decree permanently enjoined the complained of violation, and enjoined interstate operations unless and until the plant and its equipment had been cleaned, a sanitation program had been established, a qualified expert had certified to FDA that the plant met specified requirements, and necessary FDA analyses and inspections were made. In addition, a copy of the firm's sanitation control program was to be posted where all employees would see it, employees were instructed to comply with such program, and the defendants were authorized to move to vacate the decree two years after compliance had been assured. (Inj. No. 1016; S. No. 82-282-787 et al.; S.J. No. 11)

DEFENDANTS: **Midwest Biologicals, Inc., and Melvin R. Shultz**, president and treasurer, Fenton, E. Dist. Mich.; Civil No. 82-40142.

CHARGED 4-16-82 in a complaint for injunction: That the defendants manufactured, processed, packed, labeled, distributed in interstate commerce, and held for sale after shipment of interstate components certain microbiological culture media and a certain media-component (defibrinated sheep blood), which media and media-component are *in vitro* diagnostic products; that such media and media-component had been manufactured, packed and stored under circumstances that failed to conform with current good manufacturing practice—501(h); that the labeling of the culture media included expiration dates which were false and



misleading, since the articles were not useful for the period represented by those expiration dates—502(f)(1); the labeling of the culture media and the media-component lacked adequate directions for use—502(f)(1); the quality or purity of the culture media fell below its purported quality or purity, since the article contained bacterial contaminants, mold contaminants, or both—502(c); that FDA inspections had shown serious substantial deviations from good manufacturing practice; that FDA laboratory tests determined that a 50-plate sample contained bacterial and mold contaminants in 40 plates and only mold contaminants in 10 plates; and that the defendants were well aware that their activities were in violation of the law.

DISPOSITION: A consent decree of permanent injunction enjoined the complained of violations and enjoined continued operations involving interstate articles at the defendants' Fenton, Mich., plant unless and until: specified methods, facilities and controls had been established, operated and administered; adequate controls were implemented to assure the accuracy and completeness of labeling, including the articles' expiration dates; a qualified expert had certified to FDA that the specified requirements had been met and all of the articles on hand at the defendants' plant had been examined, necessary tests made, and all examined and tested articles were destroyed or brought into compliance with the law. (Inj. No. 998; S. No. 82-186-991 et al.; S.J. No. 12)

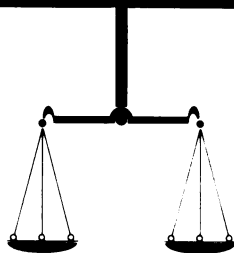
DEFENDANTS: **Pharmadyne Laboratories, Inc.**, and **Bernard A. Bedrick**, president, Elmwood Park, Dist. N.J.; Civil No. 80-1312.

CHARGED 5-8-80 in a complaint for injunction: That the defendants, at their Elmwood Park, N.J., plant, produced, packed, labeled and distributed in interstate commerce various drugs (e.g., allopurinol tablets, chlorothiazide with reserpine tablets, chlorpropamide tablets, chlorthalidone tablets, doxylamine succinate with B-6 tablets, furosemide tablets, hydroxyzine hydrochloride tablets, hydroxyzine pamoate capsules, metronidazole capsules, spironolactone tablets, spironolactone with hydrochlorothiazide tablets, triamterene with hydrochlorothiazide capsules, and trimethoprim with sulfamethoxazole tablets); that such drugs were held for sale after interstate shipment of various of their components; that such drugs were new drugs without effective approved New Drug Applications; that the labeling of such drugs failed to bear adequate directions for use and the drugs were not ex-

empted because of their new drug status; and that the defendants were well aware that their activities, in marketing new drugs without approved New Drug Applications, were in violation of the law—505(a), 502(f)(1).

DISPOSITION: Upon consent of the parties, without the admission of any facts or law, upon the agreement that the government would withdraw its request for a temporary restraining order with respect to allopurinol, chlorpropamide, diethylpropion hydrochloride, doxylamine succinate with B-6, hydroxyzine hydrochloride, hydroxyzine pamoate, metronidazole and trimethoprim with sulfamethoxazole, the defendants agreed not to distribute or ship a number of specified drugs during the pendency of the government's application for a preliminary injunction. The government's application for a temporary restraining order was denied without prejudice in all other respects; the specified drugs which the court restrained the defendants from shipping were chlorothiazide with reserpine, chlorthalidone (25 mg and 50 mg only), furosemide, prochlorperazine, spironolactone, spironolactone with hydrochlorothiazide, and triamterene with hydrochlorothiazide. The government served written interrogatories on the defendants. The defendants served a request for the production of documents on the government.

Ultimately, a consent decree of permanent injunction was entered into. The consent decree enjoined the interstate shipment, or the production (using interstate components), of any drug containing any of the following ingredients: allopurinol, chlorothiazide with reserpine, chlorpropamide, chlorthalidone, diethylpropion hydrochloride, doxylamine succinate with vitamin B-6, furosemide, hydroxyzine hydrochloride, hydroxyzine pamoate, metronidazole, prochlorperazine, spironolactone, spironolactone with hydrochlorothiazide, triamterene with hydrochlorothiazide, or trimethoprim with sulfamethoxazole, unless and until an approved New Drug Application was effective with respect to such drug or such drug was otherwise approved or exempted. Additional provisions in the decree included a requirement of notice by the defendants to FDA prior to their intended marketing of a drug on the basis that it was not a new drug, a requirement concerning destruction, embargo or bringing into compliance of specified drugs which were on hand or under the control of the defendants, and a requirement that the defendants sign consent decrees of condemnation in the seizure actions of specified drugs claimed by the defendants. (Inj. No. 948; S. No. 80-162-284 et al.; S.J. No. 13)



DEFENDANTS: **Pittston Warehouse Corp.** (a division of Pittston Stevedoring Corp.) and **Robert F. Chiarello**, president, Brooklyn, E.Dist. N.Y.; Civil No. 80-3108.

CHARGED 11-7-80 in a complaint for injunction: That defendants held foods for sale after such foods had been shipped in interstate commerce; that such foods contained rodent filth and had been held under insanitary conditions; that FDA inspections revealed specified insanitary conditions; and that the defendants were well aware of the insanitary conditions at their Brooklyn, N.Y., warehouse—402(a)(3), 402(a)(4).

DISPOSITION: A consent decree of permanent injunction enjoined the complained of violations, enjoined the defendant to select an expert to certify that the warehouse was operated so as to assure that food was not contaminated, and enjoined the defendants to examine all foods on hand at the warehouse, to have FDA make necessary analyses, and to destroy or otherwise bring into compliance all contaminated foods. (Inj. No. 1022; S. No. 78-140-783 et al.; S.J. No. 14)

MISCELLANEOUS ACTIONS

SUBJECT: Red No. 2 as a color additive and FDA's denial of its permanent listing, District of Columbia Circuit Court of Appeals, Washington, D.C.; No. 80-1403.

PETITIONED 4-14-80 by Certified Color Manufacturers Assn., Washington, D.C., against HEW Secretary Patricia R. Harris in a petition for judicial review: That the FDA commissioner's decision against permanent listing of the color additive FD&C Red No. 2 should be reversed because the commissioner had not applied the proper standard for determining color additive safety and because the commissioner's denial was not adequately and fairly supported by the administrative record.

DISPOSITION: The petitioner argued that FD&C Red No. 2 was a water-soluble food coloring that had been widely used for over 70 years, had been one of the first food colors approved under the Food and Drugs Act of 1906, and was the most thoroughly tested food color; that, after the Color Additive Amendments of 1960, FD&C Red No. 2 had continued in use as a provisionally listed color additive and, in 1969, FDA's Bureau of Foods concluded that "results of extensive toxicological and biochemical testing of FD&C Red No. 2 (amaranth) demonstrate the safety of this color additive."

However, Russian investigations on male rats conducted

between 1968 and 1970 on a substance identified as "amaranth" (FD&C Red No. 2 is known as amaranth in its nonpurified, industrial form) created a concern that FD&C Red No. 2 might be a carcinogen, although there was substantive evidence before an FAO/WHO committee that the Russian amaranth was not FD&C Red No. 2 and although both the FAO/WHO Joint Expert Committee on Food Additives and FDA's toxicologists rejected the Russian study.

In an attempt to duplicate the results of the Russian studies of amaranth, FDA began its own tests of Red No. 2. This FDA study (the Taylor/Monlux study) was an extensive long-term chronic animal feeding study that involved feeding Red No. 2 to rats whose dams had been exposed to Red No. 2 since birth. In 1976, the FDA commissioner received a statistical analysis by Dr. David W. Gaylor of the data from the ongoing Taylor/Monlux study which showed a statistically significant increase in malignant tumors in female rats in the highest dosage group. Although the provisional listing of Red No. 2 had just been extended, the commissioner proceeded to end the provisional listing; his action was affirmed in *Certified Color Manufacturers Ass'n v. Mathews*, 543 F.2d 284 (D.C. Cir. 1976); and the color additive was removed from the market.

Nevertheless, the petitioner persisted by objecting to the denial of a pending color additive petition for permanent listing of Red No. 2 and by requesting a formal hearing before an administrative law judge. On March 30, 1978, Administrative Law Judge Daniel J. Davidson found that, although the tests of Red No. 2 showed many negative results, and several equivocally positive results, the data before FDA neither established Red No. 2 as being safe nor established it as not being a carcinogen in man or animals.

The petitioner appealed to the FDA commissioner who, after review of the entire record, denied the permanent listing of Red No. 2. The petitioner then appealed to the Circuit Court of Appeals, arguing that permanent listing had been improperly denied because the commissioner had adopted a "conservative approach" requiring more proof than a reasonable certainty, and because the commissioner had selectively parsed the record rather than basing his decision "upon a fair evaluation of the entire record" as required by statute.

The Court of Appeals, without an opinion, upheld the administrative law judge and the commissioner and affirmed the denial of permanent listing of Red No. 2. (Misc. No. 584; S.J. No. 15)

DON'T DIE OF EMBARRASSMENT.

It starts quite innocently: you convince yourself the symptoms aren't serious. So if you sought medical help you'd just look foolish. And later it's too late.

Each year 350,000 Americans die from heart attacks before reaching the hospital. Often after a deadly, unnecessary delay. In fact, the average victim waits over three hours before consulting a doctor. Because he doesn't realize

what his symptoms mean. And he doesn't want to seem silly.

Please, learn the warning signals of a heart attack. And, if you experience any of them, get help. Call a paramedic at once. Or, if you can get to an emergency room faster another way, do so. Without a second thought.

After all, saving face means nothing compared to saving your life.

WARNING SIGNALS OF A HEART ATTACK

1. An uncomfortable pressure, fullness, squeezing or pain in the center of your chest behind the breastbone.
 2. The sensation may spread to your shoulders, neck or arms. If it lasts for two minutes or more, you could be having a heart attack.
 3. Severe pain, dizziness, fainting, sweating, nausea or shortness of breath may also occur, but are not always present.
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WE'RE FIGHTING FOR YOUR LIFE

