

FDA CONSUMER

• VOL. 22 NO. 1

FEBRUARY 1988 •

RESTORES
HAIR IN
SECONDS

**Quackery
Targets
Teens**

WHAMPO
BODY
WRAP



REDUCE
THIGHS
IN SECONDS

EAT 20,000
CALORIES A
DAY AND
LOSE WEIGHT





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FDA is best known as the nation's public health "cop," policing the marketplace to ensure the safety of our food, drugs and other products. Commissioner Frank Young explains that the agency also performs another vital function — educating the public about how to use those products properly.

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Inside Front Cover Photo

They may not be as vitally important as an artificial heart or an artificial kidney, but artificial fingernails are serious business to many of those who care about their appearance right down to their fingertips. For a closer look at artificial nails and some cautions on their use, turn to page 18.



Updates

Child-Proof Packaging Saves Lives

1985 marked the first year that not one child under 5 died from accidental ingestion of aspirin, the Poison Prevention Week Council announced recently.

According to Terrence M. Scanlon, chairman of the Consumer Product Safety Commission, this heartening news is directly related to child-resistant packaging. Before this packaging was required, aspirin was the largest single agent involved in accidental poisonings. In 1967, 92 children died from aspirin overdose, according to the National Center for Health Statistics. That figure dropped to 46 in 1972, the first year aspirin containers were required to be child-resistant, and aspirin deaths continued to decline over the next several years.

Childhood deaths from other drugs have also declined. In 1972, 96 children under 5 died from accidental ingestion of drugs other than aspirin. Between 1972 and 1974, as use of the safety packaging increased, the number of deaths declined sharply, and by 1984, the toll was down to 31.

The 35 members of the Poison Prevention Week Council include CPSC, FDA, the Department of Agriculture, and several trade and professional associations. This year's National Poison Prevention Week will be observed during the week of March 20.

AIDS Brochure Available

Some 45 million copies of a new Public Health Service brochure on AIDS are being distributed nationwide as part of the Department of Health and Human Services' ongoing effort to educate the public about AIDS.

The eight-page brochure, "What You Should Know About AIDS," answers questions people most frequently ask about the disease and how it is and is not spread. It is illustrated with photographs and remarks from people with first-hand knowledge of AIDS, such as family members of people with AIDS, volunteers working with AIDS patients, and AIDS researchers.

The brochures are available by writing to the U.S. Public Health Service, "America Responds to AIDS," P.O. Box 23961, Washington, D.C. 20026-3961.

For more information on the federal government's

efforts to educate the public about AIDS, see "AIDS Education" in the September 1987 *FDA Consumer*.

Transplant Drug OK'd for Wider Use

An investigational new drug called cytomegalovirus immune globulin has gained FDA's permission for use in treating kidney transplant patients. This is the first experimental drug released for treatment use under FDA's expanded "treatment-IND" regulations. Under this rule, FDA makes promising, but unproven, drugs more widely available to desperately ill patients who have no other hope. (See also *FDA Consumer*, "Experimental Drugs for the Desperately Ill," June 1987, and "Drugs for the Desperately Ill," September 1987.)

About half of the U.S. adult population has been exposed to the cytomegalovirus (CMV), but it's usually harmless because the immune system prevents infection. Following a kidney transplant, though, the recipient's immune system is suppressed to prevent rejection of the new organ. The weakened immune defenses increase a person's risk of certain infections, including CMV. If an unexposed patient receives a kidney with a dormant cytomegalovirus, a severe and uncontrolled infection throughout the body can result.

Cytomegalovirus immune globulin is made from human blood plasma (the fluid part of blood) that has a high concentration of cytomegalovirus antibodies. In clinical tests done by the manufacturer, the Massachusetts Department of Public Health, uninfected kidney transplant patients were given doses of the drug through a vein. Results of the study, reported in the Oct. 22, 1987, *New England Journal of Medicine*, suggest the drug conferred protection to the patients until their immune systems returned to normal.

FDA has not yet approved this experimental drug for commercial distribution. However, in announcing the drug's availability for kidney transplant patients last Oct. 26, FDA Commissioner Frank E. Young, M.D., Ph.D., said, "Since there are so few matched donor kidneys available and many organ donors would have encountered cytomegalovirus infection at some time in their lives, this potential exposure of transplant patients to serious infection can't usually be avoided. It is encouraging that there



now may be a product to prevent the complications of cytomegalovirus infections.”

A license application has been submitted and is currently under review. The sponsor is making the drug available initially only to transplant centers in Massachusetts, but plans to expand that availability as production capacity permits. Additional information about the drug may be obtained from the Office of Public Affairs, Massachusetts Department of Public Health, Boston, Mass. The telephone number is (617) 727-0049.

Test of Alzheimer's Drug Suspended

FDA and the manufacturer of an experimental drug for Alzheimer's disease are looking into cases of possible liver damage to see whether the problem is permanent and is actually caused by the drug. At FDA's request, the firm, Warner-Lambert Company of Morris Plains, N.Y., suspended the study of tetrahydroaminoacridine (THA) on Oct. 23, 1987, about a month after the testing had begun.

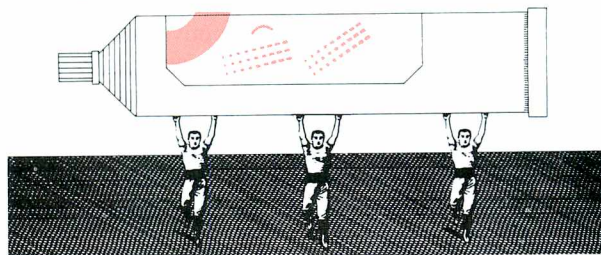
Outside experts in liver toxicity have been working with FDA and the firm in evaluating the drug. Depending on the evaluation, the agency may allow the tests in Alzheimer's patients to resume, most likely at lower dosages.

Warner-Lambert provided regular safety updates to FDA from the very start of its clinical tests with THA. Thus, when blood samples from eight patients showed high levels of liver enzymes — a sign of possible liver damage — FDA learned about it right away. Because the problem was detected so promptly, fewer than 50 of the planned 300 patients had actually been enrolled in the study. Researchers at 17 centers across the country had been conducting the study with funding from the National Institute on Aging and the Alzheimer's Disease and Related Disorders Association.

The progressive mental impairment caused by Alzheimer's disease disables about 2.5 million Americans each year. THA, one of several potential Alzheimer's therapies being tested, gained national attention when favorable results of a study of the drug at the University of California, Los Angeles, were reported in the Nov. 13, 1986, *New England Journal of Medicine*. However, subsequent letters to the journal and an FDA inspection raised ques-

tions about the design and conduct of the study. The Warner-Lambert trial was intended to assess THA's safety and effectiveness more conclusively.

Meanwhile, until the possibility of liver damage is resolved, it is particularly important that any illegally circulating THA not be used.



OTC Drug Sales to Rise

The demand for over-the-counter drugs will double — and possibly triple — by 1995, according to a report by a California research and consulting firm.

“Winning Competitive Positioning for the Coming OTC Market Eruption” by SRI International predicts that annual sales of OTC drugs will grow from \$8.6 billion in 1986 to \$18 billion, and possibly as high as \$23 billion, by 1995. Reasons for this growth include the development of new products and regulatory changes that have allowed a number of drugs to switch from prescription to OTC status. In addition, the report says greater consumer interest in health and preventive medicine will increase the demand for OTC drugs over the next 10 years.

Product categories covered in the report include internal analgesics, antacids and antiflatulents, laxatives and antidiarrheals, appetite suppressants, cough, cold and allergy remedies, topicals, nutritional supplements, and an “all other” category that includes sleep aids, stimulants and antiemetics.

New IUD Available Soon

An intrauterine device approved by FDA in 1984 will be available for the first time in the United States early this year, according to an international organization for family planning.

The Population Council of New York recently



Updates (Continued)

announced that it had negotiated a licensing agreement with GynoMed Pharmaceuticals Inc. of Somerville, N.J., to sell the Copper T 380A IUD to American women. Although this IUD has never been available before in the United States, it has been provided by the U.S. Agency for International Development to family planning programs in developing countries.

Introduction of this device will once again give American women a choice of IUDs. Since G.D. Searle withdrew its two copper-wound IUDs from the market in January 1986, the only IUD available in the United States has been the Progestasert Intrauterine Contraceptive System, an IUD that uses progesterone to help prevent pregnancy.

According to the Population Council, clinical trials in the United States show a failure rate for the Copper T 380A of about 1 per 100 women over 25 who used the device for a year. The council said this rate places the Copper T 380A among the most effective contraceptives in the world.

Before the IUD can be distributed in this country, FDA must review and approve the physician and patient labeling. The agency requires that a leaflet detailing the risks, benefits and proper use of the device be given to every woman who plans to use it. In addition, FDA recommends that women discuss with their physicians the use of any IUD to be sure they understand the risks of infection and possible permanent infertility associated with IUD use.

Because of these risks, GynoMed said it will not recommend use of the Copper T 380A for women who are under 25, have never had children, or who have more than one sexual partner.

Nuclear Scans Increasing

More and more people who have had heart problems or suffered head injuries will have the extent of the damage diagnosed by nuclear medicine, according to a study by a New York market research firm.

A Frost & Sullivan, Inc., study says that new brain scans, which are still under development, along with the increasing use of radiopharmaceuticals (radioactive chemicals) in cardiac imaging will account for much of the growth in nuclear medicine. In addition, the number of bone scans done each year is also growing. About 9 million individual nuclear scans are performed in a year, the study says.

Nuclear medicine scans, like conventional X-rays, use very small amounts of radiation. But, unlike X-rays, in

which the radiation passes through the body from an outside source, nuclear scans use a radiopharmaceutical placed within the body. A special instrument is used to detect the radiation given off by the drug and convert it to an image that can be photographed or displayed on a television screen. (Another form of nuclear medicine involves mixing the radioactive chemical with a sample of blood or urine from the patient for analysis in a laboratory.)

The study predicts that sales of radiopharmaceuticals will go from \$126 million in 1987 to \$167 million by 1991. Sales of the instruments used to detect the radiation — for example, rotational cameras used in emission computed tomography (ECT) and positron emission tomography (PET) scanners — will rise from \$199 million to \$245 million during that same period.

For more information on nuclear medicine, see "Using Medical Radiation from the Inside Out" in the July–August 1987 *FDA Consumer*.

Court Rejects Colors

The U.S. Court of Appeals for the District of Columbia has ruled that FDA does not have legal authority to approve color additives that induce cancer in laboratory animals, however slight the risk to humans. The ruling was in response to a challenge by Public Citizen Inc.

In a unanimous decision, the three-judge court said that the risks posed by two color additives — D&C Orange No. 17 and D&C Red No. 19 — are admittedly trivial. However, the court said that the Delaney Clause for color additives made no exceptions for a trivial, or "de minimus," carcinogenic risk. (The Delaney Clause of the Federal Food, Drug, and Cosmetic Act prohibits the approval of any color additive found by appropriate test to induce cancer in man or animal.)

FDA approved D&C Red No. 19 and D&C Orange No. 17 for external use in cosmetics and drugs in August 1986 based on conservative risk assessment and analysis by a panel of scientific experts from five government agencies. Although the colors caused cancer when ingested by animals, the panel estimated that the risk of any one individual getting cancer in his or her lifetime from the colors was 1 in 9 million for Red No. 19 and 1 in 19 billion for Orange No. 17. The agency concluded that the theoretical risk is so trivial as to pose no risk at all. The court said that if FDA believes that this risk ought to be tolerated, the agency should seek to have the law changed.

In a related case, the court ruled that FDA could con-



tinue to provisionally list, or allow the use of, three other color additives — FD&C Red No. 3, D&C Red No. 33, and D&C Red No. 36 — pending a decision on whether the scientific evidence allows them to be approved.

Food Allergies: Avoid the Offenders

The best treatment for a known or suspected food allergy is simply to avoid the offending food, according to a study done at the Johns Hopkins Medical Institutions and reported in the Nov. 27, 1987, *Journal of the American Medical Association*. Food allergies are rarer than generally believed and difficult to diagnose. The study recommends a carefully taken patient history, perhaps aided by skin tests and a radioallergosorbent test (RAST), which measures antibody to specific substances. Cell toxicity tests using blood cells and food substances have no value. Food allergies can cause stomach and intestinal disturbances, as well as hives and swelling from water retention, and even the severe hypersensitive reaction of anaphylaxis, which in extreme cases can lead to death. (See "Food Allergies: Separating 'Hype' from Fact," *FDA Consumer*, June 1986.)

Reprints Available

Reprints are available of the following articles that appeared recently in *FDA Consumer*: "Defrauding the Desperate: Quackery and AIDS" from the October 1987 issue and "Athletes and Steroids: Playing a Deadly Game" from the November 1987 issue.

Reprints can be obtained from the Food and Drug Administration, HFI-40, 5600 Fishers Lane, Rockville, Md. 20857. Up to 200 copies will be provided. Negatives are also available for those who need more than 200 copies.

Correction: Lovastatin

A sentence in an article about new drug development titled "The Beginnings: Laboratory and Animal Studies" in the November 1987 *FDA Consumer* incorrectly identified the developer of the cholesterol-lowering drug lovastatin. Merck Sharp & Dohme of West Point, Pa., is the developer.

Consumer Forum

Athletes and Vitamin Supplements

In the May 1987 "Consumer Forum," Dr. Mennen misperceives the significance of the Moffatt article (*Journal of the American Dietetic Association*, November 1984). Moffatt's statement that the diets of a group [of teenage gymnasts] "appear nutritionally inadequate" is a misperception derived by comparing the nutrient content in the diets to the Recommended Dietary Allowances (RDAs). The statement ignores that the RDAs are specifically set well above the needs of anybody to allow an adequate margin for storage.

The editorial comment by *FDA Consumer* below the Mennen letter referred to the *Dietary Guidelines for Americans*, but did not mention the most pertinent comment in those dietary guidelines, which is, "you will rarely need to take vitamin or mineral supplements if you eat a variety of foods."

Dr. Mennen has indicated a particular interest in reality with respect to supplementation. That reality is delineated

in "Vitamin Preparations as Dietary Supplements and as Therapeutic Agents," from the Council on Scientific Affairs of the American Medical Association (*Journal of the American Medical Association* 257:1929-36, 1987), which states, "Healthy adult men and healthy adult non-pregnant, non-lactating women consuming a usual, varied diet do not need vitamin supplements. Infants may need dietary supplements at given times, as may pregnant and lactating women. Occasionally, vitamin supplements may be useful for people with unusual lifestyles or modified diets, including certain weight reduction regimens and strict vegetarian diets."

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Health Talk With Dr. Frank Young

Spreading the Word: FDA as Health Educator

by Frank E. Young, M.D., Ph.D., Commissioner of Food and Drugs

FDA is probably best known for its role in removing potentially dangerous products from the marketplace. In fiscal year 1987 alone, for example, FDA monitored approximately 2,400 recalls and instituted 200 seizures of contaminated foods, unsafe or ineffective drugs, and defective medical devices.

I think the public knows less about how FDA confronts public health problems that result from products that are properly manufactured, but are improperly used. Some examples: Adverse drug reactions can occur when a patient doesn't take a medication according to the doctor's instructions. If milk is improperly handled, it can become contaminated with bacteria and lead to an outbreak of food poisoning. When an anesthetist fails to properly set up and check equipment, patients can be injured or killed. In fact, the majority of anesthesia injuries have been attributed to either user error or a combination of user and machine errors.

Because these are problems linked more to people's behavior than to product flaws, the key to solving them is *education*. And here FDA has a critical role to play. Once the agency has identified the cause of the problem as being user-related rather than product-related, FDA must use education to alert the right people and provide them with the information they need to correct the situation. In fact, FDA's role as an educator is so important that expanding this function is one of 11 major goals in Phase II of our Action Plan—our “navigation chart” to guide the agency into the 21st century.

While FDA's educational role is now getting special attention, the agency has a tradition of using this tool as effectively as it has its regulatory and legal options. This is especially true when it comes to getting the word out to the general public. A survey last year by the federal Consumer Information Center in Pueblo, Colo., found that 9 of the 20 most frequently requested consumer publications were from FDA. (In fact, all of those publications originally were published as articles in *FDA Consumer*.) Let me give you a few examples of how FDA has protected the public health by “spreading the word”:

- *AIDS Education*—FDA has taken an active role in educating both the public and the medical community about acquired immune deficiency syndrome, or AIDS. We issue monthly updates on the status of AIDS drugs under development and review; we present special AIDS exhibits at health professional meetings; and we've published special AIDS issues of *FDA Consumer* and the *FDA Drug Bulletin*, which is sent to over a million doctors and other health professionals. Our Center for Devices and Radiological Health is also working with the Centers for Disease Control and the Public Health Service's Task Force on AIDS to inform the public about the proper use of condoms as one way to help prevent the spread of the AIDS virus. Clearly, until a vaccine or a cure can be found, education about prevention and treatment is our mightiest weapon against this deadly disease.

- *Special Messages for Teenagers*—The abuse of powerful steroid drugs by body builders and athletes—some of them only in their early teens—is a great concern to FDA. While we work with other law enforcement agencies to shut down illegal steroid operations, we also are sending the message of the dangers of steroid abuse to coaches and the athletes themselves, in hopes that a little knowledge will help them help themselves.

We've also been reaching the nation's high school students with other important messages in the form of innovative, two-sided “learning units.” One side is a colorful, informative poster that can be displayed on bulletin boards or in classrooms. The other side provides the teacher with material that can be taught in class. One of the learning units concerns the hazards of indoor tanning, stressing the long-term risk of skin cancer and counteracting misleading claims about “safe” tanning. Another learning unit alerts young women to the possible link between highly absorbent menstrual tampons and toxic shock syndrome (TSS), a rare but potentially fatal condition. The unit explains how to minimize the risk of TSS and what to do if symptoms occur.

- *Nutrition Information*—Although education can sometimes substitute for regulation in solving a public health problem, there are other times when the best way to educate the public is by means of a regulation. Nutrition information on food labels is a case in point. Since 1973, FDA has required that detailed information on the nutrient content of a food be shown on the label if nutrients have been added to the product or if a nutrition claim—“fewer calories,” for example—is made. Some 55 percent of all foods that come under FDA's jurisdiction now carry nutrition labeling.

In 1986, because of concern about the link between sodium and high blood pressure, FDA began requiring that nutrition labeling include the amount of sodium (usually found as salt) in the product. That labeling information, combined with a major public education campaign by FDA, the U.S. Department of Agriculture, and others, has had a dramatic effect on Americans' diets. According to recent surveys, sodium (or salt, which is 40 percent sodium) is the ingredient people say they are now avoiding the most: Forty-four percent say they're trying to consume less sodium, up from 14 percent in 1978.

Another major change in food nutrition labeling has been proposed by FDA to reflect the growing consensus among health experts that Americans can lower their risk of heart disease by eating less fat—particularly saturated fat—and cholesterol. In November 1986, FDA proposed to include information about fat and cholesterol content whenever a food label makes claims that a food is lower in cholesterol or cholesterol-free. This would help consumers find products with less cholesterol as part of a “healthy heart” diet.

In a more novel attempt to convey accurate nutrition information, FDA proposed last August to allow manufacturers to place

The Darker Side of Indoor Tanning

Skin Cancer
Eye Damage
Skin Aging
Allergic Reactions



This poster is one side of a "learning unit" sent to schools by FDA to help warn teenagers about the hazards of sunlamps and tanning booths. The other side provides information on tanning that teachers can use in class.

health-related messages on food packages. The messages, which would have to be based on widely accepted scientific data, would inform consumers about the health benefits that a particular type of food provides. FDA will weigh public comments on its proposal before publishing a final rule.

- **Drug Evaluation**—Consumers—as patients or potential patients—need to understand the difficult and time-consuming process by which important new drugs are developed, tested, and brought to market in the United States. Those who do understand the process will be less vulnerable to false hopes and better able to realistically gauge the value of so-called "breakthrough" drugs they may learn of through the news media. To that end, *FDA Consumer* has been running a series of articles (which concludes in this issue) about new drug development. FDA will use other outlets as well to help educate consumers about this process, which affects virtually all of us at some time during our lives.

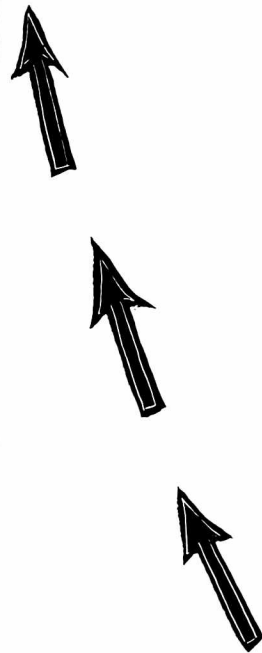
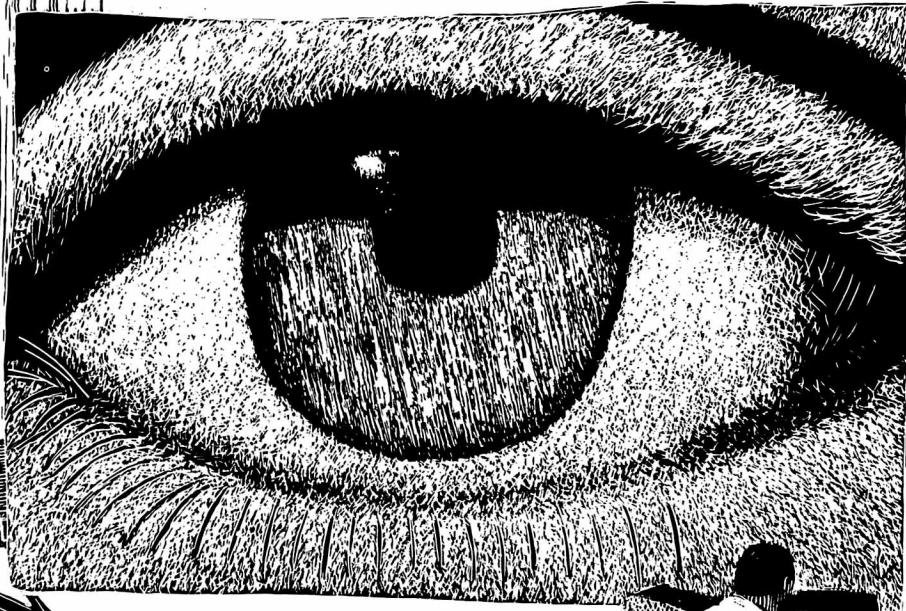
- **Informing Health Professionals**—It's sometimes not enough to reach just the general public. FDA also has a responsibility to be sure that health professionals have the latest information on using medical products safely and effectively. This kind of education is often carried out jointly with the medical profession and manufacturers. For example, working with the American Society of Anesthesiologists and equipment manufacturers, FDA developed an educational program on anesthesia safety for doctors and nurses. It consists of a series of instructional videotapes and a pre-anesthesia checklist (like the pre-flight checklist used by airline pilots). The tapes have been sent to every anesthesia training program in the United States, and the checklist has reached

virtually every anesthesiologist and nurse anesthetist in the country.

- **Educating Industry**—FDA also takes pains to inform regulated industries about legal requirements, policies and procedures. For many years, FDA's Center for Veterinary Medicine has counseled on the proper use of veterinary drugs in food animals. Our main concern here is to avoid harmful residues of those drugs showing up in meat, eggs or milk. One of the most effective tools for getting our message across is our *FDA Veterinarian* newsletter. Almost 7,000 livestock producers, veterinarians, animal drug manufacturers, feed mills, and other parts of the agribusiness industry subscribe to the newsletter. We also reach these groups through farm-oriented magazines, professional journals, and radio and TV interviews and public service announcements.

Similarly, we are working to help pharmaceutical companies prepare high-quality applications for submission to FDA for new drug approvals. These applications include, among other things, the results of the tests that have been done of the drug in humans, and they generally contain many thousands of pages of data. So, a well-prepared application has a distinct advantage in moving quickly through FDA's review. In fact, we've found that some 10 to 18 months can be shaved off the review time if an application doesn't have to be returned to the company for additional work. (It takes an average of about two years for FDA to review a new drug application.) Thus, our educational efforts can lead to significant public health benefits. As part of this educational program, we issued 12 guidelines last year on how to prepare new drug applications and held seminars with manufacturers to explain the guidelines.

I believe these few examples show just how important FDA's educational role is, whether our audience is doctors, drug manufacturers, food producers, or consumers. As a former educator myself, I am confident that the knowledge we can share is often just as powerful a tool in protecting the public health as regulations or legal actions—and sometimes a far more effective one, for it can truly change behavior. ■



Watching for Problems That Testing May Have Missed

by Stephen J. Ackerman

“Jane” is 71 years old; she weighs just 100 pounds. She works mornings in a Washington, D.C., office, then travels to a Virginia nursing home to care for her husband, a victim of Alzheimer’s disease. When she came down with shingles (herpes zoster, a viral irritation of the nerve endings), her doctor prescribed a painkiller he had used successfully in patients for 20 years so she could keep up her routine.

When Jane took the prescribed dose at work, something went wrong. So violent were her dizziness and nausea that her colleagues rushed her to a nearby emergency room. She was given an electrocardiogram, intravenous fluids, and a sedative injection. After five hours, she still needed help in getting home, and she was still groggy a week later.

Now recovered, Jane blames herself for not being more careful. With her small frame, she’d had milder reactions to adult doses of both prescription and nonprescription drugs in the past. She feels she should have reminded her long-time physician of this when he wrote the prescription. She wonders whether adult drug dosages shouldn’t be modified to take into account the patient’s health, weight and age.

Jane isn’t alone. In 1986 FDA received over 53,000 reports of adverse reactions to drugs. While many reactions are mild, some are serious indeed; more than 12,000 deaths or hospitalizations suspected of being related to reactions to drugs are reported yearly. (Not all of these suspected reactions are confirmed.)

NO ABSOLUTE SAFETY

Do these reports mean that the drug approval process is flawed? Do drug manufacturers put products on the market and then hold their breath to see if they really work? Doesn’t a drug’s approval mean that it’s absolutely safe? The answer to all these questions is no. A closer look at the numbers shows that adverse drug reactions occur in just a small percentage of the 2.3 billion inpatient and outpatient prescriptions filled annually. Moreover, a drug’s development

process doesn’t end when it is marketed; in a sense, it never really ends at all.

Let’s look at what happens when—after perhaps a decade of development costing millions of dollars, testing on thousands of volunteers, and rigorous evaluation of the results by FDA—a new drug is finally approved for general use.

Even the most extensive pre-market testing can never cover all possible circumstances. Testing perhaps 3,000 people over a period of months or even a few years won’t always identify a rare reaction unfolding over a long time, or affecting perhaps just one person in 10,000. Furthermore, drugs are rarely tested in such potentially vulnerable groups as the elderly, and never among pregnant women. Consequently, not every reaction can be foreseen for the entire population; groups in whom a drug has not been tested must be particularly cautious in using it.

A case in point is diethylstilbestrol (DES), widely prescribed in the 1950s and 1960s to prevent miscarriages. The vaginal tumors caused by this drug only began to show up in the daughters of DES users more than 15 years later. Mercifully, such cases are uncommon.

Side effects and adverse reactions that show up in testing before a drug goes on the market are noted in the instructions that physicians (and, in some cases, patients) receive. But in some circumstances, FDA approves drugs with the condition that continuing studies of their safety be carried on to uncover rare or long-term reactions. The anti-cholesterol drug lopid and the Copper-7 intrauterine contraceptive first reached the market in that way.

For all drugs, to minimize the chances of unforeseen disaster and to take advantage of any new benefits a product may reveal, the drug development process continues after FDA approval in the form of “Post-Marketing Surveillance.”

POST-MARKETING SURVEILLANCE

FDA and the pharmaceutical industry closely monitor drug products on the market. On the most basic level, FDA agents around the country inspect factories regularly to ensure good manufacturing and laboratory practices which

guarantee that the drugs we buy are pure, properly compounded, and accurately labeled. In addition, both FDA and manufacturers collect reports of adverse drug reactions. Drug firms must report all reactions they learn of to FDA. Serious ones must be reported quickly; others may be sent in quarterly or annually. A serious reaction is one that causes hospitalization (or which prolongs a hospital stay), or results in permanent disability or death. Reactions involving deliberate or accidental overdose, cancer, or birth defects are always regarded as serious. If a manufacturer notes an increased frequency of reactions—that is, more than anticipated from earlier testing—this increase also must be reported within 15 days.

FDA quickly puts all reports into a computer and then searches for any significant patterns. Should an important new toxicity problem emerge and be confirmed, FDA and the industry have several options. One is to change the directions for the product to reduce the dose or warn certain vulnerable groups of people.

In urgent and unusual circumstances, products may be withdrawn from the market, either voluntarily by the manufacturer or by FDA order. The example of one product illustrates how FDA and industry can use information gained from reaction reports to speed protection of the public. In January 1986, the anti-inflammatory drug suprofen, newly approved to treat arthritis, reached the U.S. market. By mid-March, half a dozen adverse reaction reports alerted FDA and the manufacturer to a possible connection with “flank pain syndrome,” a serious side effect involving severe pain and kidney problems. By April, a “Dear Doctor” letter notified 170,000 physicians of the situation. Three other “Dear Doctor” letters and two *FDA Drug Bulletin* articles followed. The product’s instructions were changed to reduce suprofen to a drug of second choice. The consequent drop-off in its use was steep and sudden, resulting in its virtual disuse by the time it was formally taken off the market by its manufacturer some months later. Although the product had been on the market in Europe for four years, prompt reaction reporting enabled FDA

to determine the seriousness of a previously unnoticed side effect in just four months.

REPORTING DRUG REACTIONS

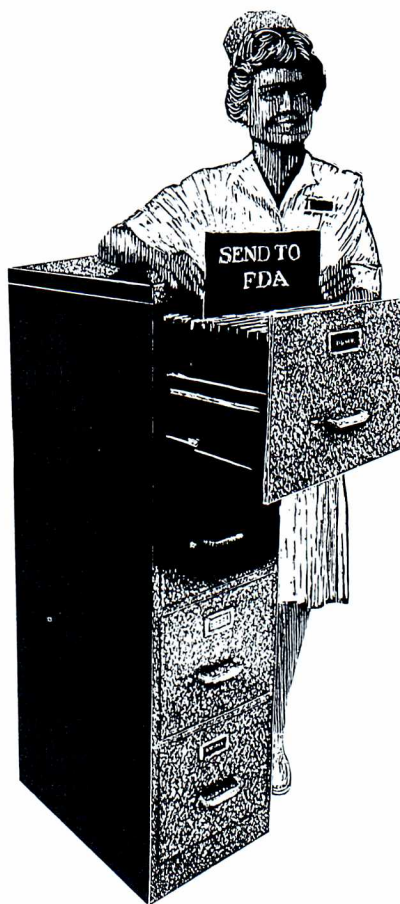
To help track the performance of their products, many drug firms rely on their sales personnel. These "detail" men and women not only sell products, but also elicit information from the health-care providers they visit. They must report back to their firms the product information they glean in their travels. "We get about half of our ADR [adverse drug reaction] reports from our own representatives," says Merck, Sharp & Dohme's director of epidemiology, Dr. Robert E. Damiano, as he leafs through a two-inch thick computer printout mapping the performance of one product. "They're very thorough and professional."

The other principal source of reports, both for FDA and for industry, is physicians who report directly. In the United States, their cooperation is entirely voluntary; no law requires them to report the reactions they observe. Few believe that imposing a reporting requirement would be effective; in Sweden, even though required to do so by law, doctors report only about a third of the adverse reactions they observe.

Since it means faster, more effective response to unforeseen reactions, industry and government encourage more adverse reaction reporting by doctors and other health professionals. "We like to give them something in return for contacting us," says Hoffmann-La Roche's director of drug safety, Dr. James Labraico. His firm offers doctors who report reactions up-to-date information about other reports, treatments, and statistical patterns on drug problems.

Like FDA, manufacturers want to analyze reaction reports promptly to detect any problems and gain new information about the effects of products in various patient populations. Merck, Sharp & Dohme employs three teams headed by physicians to oversee drug reports, with an internal alert system and an in-house quarterly report. In what it calls a "major serious event," the firm might notify practitioners by letter, contact them through the sales staff, or both.

Such monitoring isn't just "damage control," since the reports aren't always bad. Sometimes the wider use of drugs



on the market reveals beneficial uses that were not evident during testing. For instance, minoxidil, approved to treat high blood pressure, turned out to stimulate hair growth in some users; now it is being tested as a hair restorer. Beta blockers developed for use against angina are now being used against hypertension.

Likewise, news reports indicate that Naltrexone, a drug approved for treatment of heroin addicts, may be effective against Kaposi's sarcoma, a cancer associated with AIDS (acquired immune deficiency syndrome). In this case, the drug seems to have been used without formal testing or notifying FDA. Apparently, physicians who noted the drug's effects on the immune system used it, with their patients' consent, to treat this AIDS-related condition. This is possible—and legal—because once FDA has released a drug into the marketplace, there is no law requiring that physicians dispense it only for approved uses.

BALANCING RISKS AND BENEFITS

Does a system that expects marketed drugs to have unforeseen problems make consumers of these drugs "guinea

pigs"? Hardly. Unlike controlled experiments, public use of a drug necessarily brings it into contact with a greater variety of patients. Our specific age, sex, diet, habits, overall health, and even genetic background are just a few of the conditions the drug may not have encountered in testing.

There is an element of risk involved in taking any drug, no matter how common. Although it has passed through a rigorous approval process, a drug strong enough to require a prescription—especially a new product—obviously must be approached with caution. In most cases, a product appropriately prescribed and taken according to instructions will be quite safe. That a drug is approved for marketing, however, does not guarantee that it is absolutely risk-free.

Indeed, widespread public expectation of a 100 percent risk-free drug could ultimately chill new drug development. "We're concerned that the demand for absolute certainty about all properties of a drug prior to approval could stifle drug development throughout the industry," one pharmaceutical official confides. He notes that the threat of lawsuits could cause many firms to shun work on drugs that are needed, but have a high potential for side effects, such as antihypertensive products. "The temptation could be for firms to restrict their research and development to relatively low-risk areas," adds a consumer advocate.

IMPROVING THE PROCESS

Many observers in government, industry, and the consumer movement believe that the United States enjoys the best drug development and surveillance in the world. A number of nations simply adopt stringent American drug decisions as their own policies. Yet the same observers concede that there is room for improvement.

Although basically sound, the adverse reaction reporting system can be circumvented. Of course, it would be suicidal for a firm to suppress reports, since in time a drug's shortcomings will inevitably come out. Nonetheless, such cases have occurred. Pharmaceutical officials who failed to report adverse reactions caused by the blood pressure drug Sclerolacryn, marketed in the early 1980s, were sent to prison. Although the incidents of deliberate deception of FDA

tend to draw headlines, they are uncommon.

In fact, many believe that current FDA reporting requirements yield too much data, mixing significant information in a mountain of trivia. Some suggest that after a drug's first few years on the market, the requirement to report a drug's routine, expected reactions could be dropped, leaving changes in frequency or seriousness of reactions to stand out.

Nonetheless, the major weakness of the post-marketing surveillance system is the under-reporting of adverse drug reactions by physicians. Fewer than 10 percent of doctors report reactions they have observed, and even these report only a fraction of what they see. "Reporting a problem with a drug is as important as reporting a fire," insists Victoria Leonard of the Women's Health Network. Yet pilot projects by Rhode Island, Maryland, Massachusetts, Mississippi and Colorado under the aus-

pices of FDA reveal widespread unawareness and disuse of FDA's reporting system. Only 55 percent of doctors were aware of the system—despite regular reminders from the *FDA Drug Bulletin*, which is mailed to virtually every U.S. physician—and only 40 percent knew how to use it.

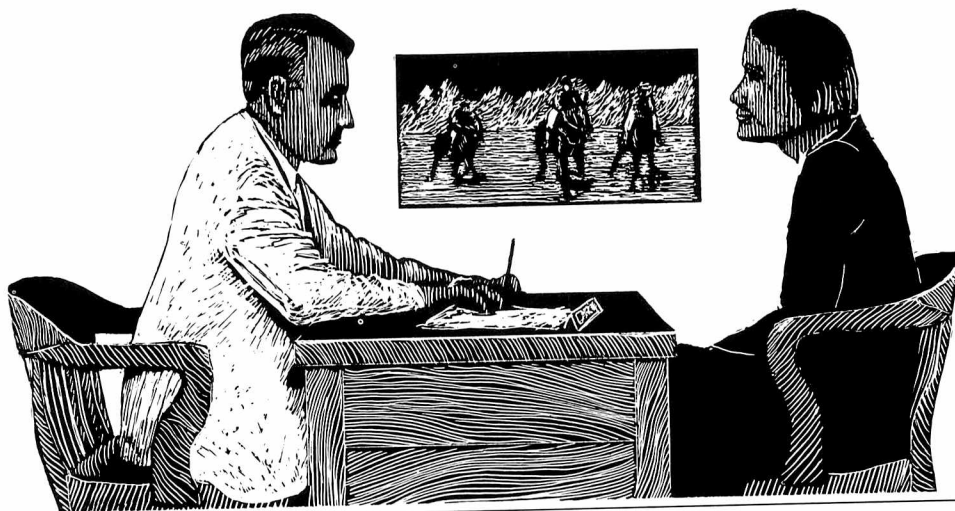
Dr. Gerald Faich, director of post-marketing drug surveillance in FDA, believes that better reporting by doctors is long overdue. The state pilot projects show that by making drug reaction reporting better understood (through meetings and bulletins for doctors), easier (by means of hot lines and third-party reporting), and more rewarding (by returning useful information), significant increases in reporting are possible. More reporting by other health professionals like nurses and pharmacists can also help speed vital feedback about drug reactions.

In fact, steps are being taken along these lines, and the results are encourag-

ing. Maryland and Rhode Island achieved fourfold increases in adverse drug reaction reporting in the first year of their promotional efforts. In its first three weeks, the Mississippi project yielded more than half the number of reports FDA received from that state during the entire previous year. A 10 percent increase in reports nationwide in 1986 seems to reflect not an increased number of adverse reactions, but increased reporting. Better still, industry is finding a gradual long-term increase in reports it receives. Such steps can only improve what FDA Commissioner Frank E. Young, M.D., Ph.D., calls "the best post-marketing surveillance system in the world." And that's the bottom line: Better reporting ultimately helps the patients who experience adverse drug reactions. ■

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Avoiding Problems With Your Medications



You can help avoid problems with your medications by following these suggestions:

- Properly taken, most medicines are remarkably safe. When you get a prescription, make sure your doctor is aware of any other drugs you are taking. If you have more than one doctor and, perhaps, a dentist prescribing for you, let each know what the others have prescribed. A drug safe when taken alone might interact badly in combination with another. Mention any nonprescription medicines and whether you drink alcoholic beverages, too. Your doctor may have to be

reminded of allergies, other medical conditions, or a history of problems tolerating drugs.

- Ask your doctor how long the drug has been on the market and what side effects it can produce. Some physicians simply won't prescribe a drug until it has been in use for a couple of years, long enough to reveal unsuspected problems.
- When you take a drug, follow instructions exactly. Many over-the-counter and some prescription drugs come with a package insert you should save, since it can help you deal with possible reactions you could have to the medication.

- Never share prescription drugs with others for whom they were not prescribed.

- If you suspect you are having an adverse reaction to a drug, call your doctor or pharmacist at once and stop taking the drug immediately. A serious reaction demands immediate medical attention. Don't be shy in seeking it.

- Ask your doctor or pharmacist to report any adverse reaction to the drug's manufacturer or to FDA directly. The quicker FDA receives a report of a drug reaction from a health professional, the sooner it can respond. ■

Medicine's 'Orphans': Drugs for Rare Diseases

by Egon Weck

The school grades of 18-year-old Katie (not her real name) had fallen precipitously. Six months earlier she had been getting A's. Now she had an F and found the best she could manage was a C.

"I was depressed and lethargic. I found it hard to go to class and hard to concentrate," Katie recalls as she looks back on 1981 and her senior year at an academically demanding prep school. Friends noticed that Katie, whom they had known as a slim, attractive, outgoing overachiever, had become overweight, withdrawn and frumpy. She seemed to have a strange odor about her, and neither family nor friends could figure out what was causing the dramatic changes.

After counseling failed, her family doctor checked her physical condition and found she had a low white blood cell count and an enlarged spleen. The physician, deciding that Katie's problem stemmed from the enlarged spleen, quickly hospitalized her for surgery. But in the course of the operation to remove her spleen, doctors found that she had cirrhosis of the liver.

On the evening after Katie's operation, a specialist in internal medicine who had attended her in the hospital puzzled over her condition. Gradually, the cirrhosis together with psychiatric and neurologic symptoms fell into place. "Of course," he thought. "Katie has Wilson's disease." (Ironically, the enlarged spleen, which precipitated discovery of the cirrhosis, was totally unrelated to the Wilson's disease.)

Doctors rarely see a case of Wilson's disease because it afflicts only about 8,000 persons in the United States. "It's so rare that doctors almost never think of the possibility, and so Wilson's disease is often missed," explains Dr. I. Herbert Scheinberg, a specialist in Wilson's disease at New York's Albert Einstein College of Medicine.

Wilson's disease afflicts people who have inherited two recessive genes—one from each parent—that prevent the body from ridding itself of excess amounts of copper. Minute amounts of copper are essential to normal body function, and the element is plentiful in foods such as broccoli, chocolate and mushrooms. With an overabundance of copper in the average American diet, however, it tends to build up to toxic levels in people who cannot eliminate it.

When Wilson's disease is left untreated, copper deposits—which form in the red blood cells, kidney, liver, brain and eyes—irreversibly damage these tissues, leading to much suffering and ultimately death by the time the patient reaches 30.

Many patients who, like Katie, suffer from rare diseases had little hope in 1981 because far more prevalent diseases like cancer were winning medical research dollars. In the case of

Wilson's disease, however, much research had been done. And in 1983 President Reagan signed a new Orphan Drug Act, which ultimately helped people like Katie because it specifically targets hundreds of rare diseases such as Wilson's.

Because Wilson's disease is often overlooked or mistaken for other conditions, such as hepatitis, multiple sclerosis, Parkinson's disease, or psychiatric problems, medical specialists estimate that only about 1,000 cases are under treatment.

Fortunately, a diagnostic test and the presence of certain physical signs enable the physician to differentiate these disorders from Wilson's. First, a deficiency in ceruloplasmin—a blood protein that transports copper—can be detected in blood tests in 96 percent of patients with Wilson's disease. Second, telltale golden-brown or green "Kayser-Fleischer" rings appear in the corneas (the protective covering over the lens) of the patients' eyes.

Other signs of Wilson's disease include a husky or barely audible voice; slurred or indistinct speech; stiff, distorted hands or feet; tremors such as head shaking, quivering legs, or flapping arms; loss of balance and difficulty walking; depression; impulsive emotional or sexual behavior; excessive salivation or drooling; and hepatitis.

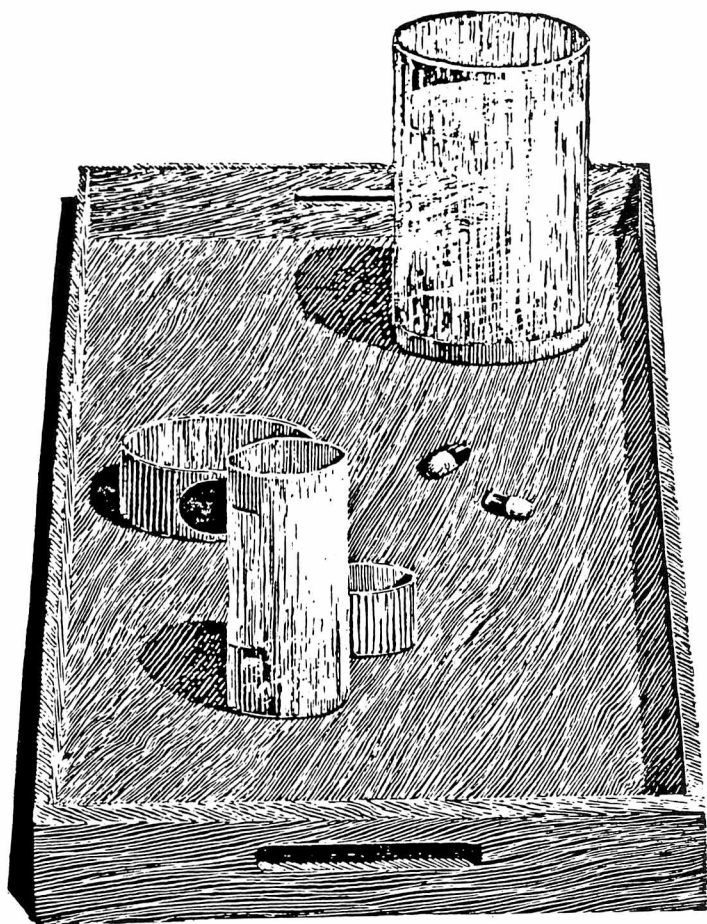
"When Katie first came in to see me," Dr. Scheinberg recalls, "Kayser-Fleischer rings were visible around the entire circumference of her corneas, and they extended from the edge about a third of the way into the center of the pupils." Often it takes an ophthalmologist using an instrument called a slit-lamp to identify the ring. In Katie's case, however, it was easily visible to the naked eye.

Today, virtually all cases of Wilson's disease can be treated effectively with one of two drugs. But what incentives are there for a pharmaceutical company to undertake the costly effort of developing a drug for such a rare disease—an effort that the pharmaceutical industry says now costs an average of \$125 million for each genuinely new drug developed?

A rare disease has been defined as one that affects less than 200,000 Americans. There are an estimated 2,000 such diseases. Years ago, when the prospects of treating rare diseases were dimmer, the drug industry itself provided what companies called "public service products" for some of them.

In 1964, for example, a Pharmaceutical Manufacturers Association (PMA) survey of member companies found there were 35 public service products being made by member firms. By 1969 the list had grown to 92 products supplied by 26 firms in the association.

Hoffmann-La Roche, for example, has developed about a half dozen drugs for rare disorders on its own initiative, and



the company continues to develop such drugs relying on its own resources.

For years, government health authorities had been aware of the plight of rare disease victims and have worked with medical researchers and companies to help them. Then, in 1973, the Interagency Committee on Drugs of Limited Commercial Value was appointed to monitor needs and propose economic incentives that would encourage the development of drugs for rare diseases. Informal contacts between the federal government and the private sector gradually led to establishment of an office on orphan products in FDA and the Commission on Drugs for Rare Diseases in the private sector.

In 1981, the plight of children afflicted with another rare disease—Tourette's syndrome—generated nationwide publicity. This disorder is characterized by bizarre, physical and vocal tics that wax and wane throughout childhood and adult life.

While a drug to treat Tourette's—haloperidol—was available, it was not effective in all patients. A second drug—pimozide, produced by McNeil Pharmaceutical—was being used abroad and in Canada, but had not been approved by FDA for use in the United States, largely because the necessary research would have been prohibitively expensive, considering the small patient population. (Pimozide was eventually approved under the incentives of the 1983 Orphan Drug Act.)

The publicity on Tourette's syndrome had great impact. It focused public attention on rare diseases generally. And it galvanized voluntary health agencies that, in turn, appealed to Congress for help.

The term "orphan drugs," first appeared in print in a 1968

editorial in the *American Journal of Hospital Pharmacy* titled "Homeless or Orphan Drugs."

"The naming of drugs for rare diseases as 'orphan drugs' was not done frivolously," Congressman Henry Waxman, D-Calif., a cosponsor of the Orphan Drug Act, has observed. "They are very much like children who have no parents, and they require special effort."

To increase recognition of the problem, the Food and Drug Administration in 1982 set up an Office of Orphan Products Development. Orphan products, according to FDA's definition, include drugs, biologics such as vaccines, medical devices, and medicinal foods to treat uncommon diseases.

The office was assigned the task of identifying promising new therapies for rare diseases and commercial sponsors to develop the products. In Katie's case, penicillamine, a drug that controls Wilson's disease, had been developed well before 1982. A prominent pharmaceutical company, Merck, Sharp & Dohme, was already manufacturing it.

Katie was put on penicillamine, but after nine months she developed proteinuria, a loss of protein in the urine that can lead to kidney failure. "Proteinuria," Dr. Scheinberg explains, "is one of the commonest of several toxic effects of penicillamine therapy and occurs in about 5 percent to 10 percent of patients." So Katie had to be taken off the drug. As a consequence, in a few months her depression returned.

"Earlier, there would have been no hope for Katie," Dr. Scheinberg explains, "and she would have been condemned to die as a young adult."

But by the time Katie came to Dr. Scheinberg, he had a new experimental drug for Wilson's disease. Developed by Dr. John Walshe at the University of Cambridge in England, the drug, trientine, lacks the toxic effect of penicillamine. After a few months on trientine, Katie's depression vanished. She continued to improve, and, in 1986, she graduated from Harvard University magna cum laude.

In 1982, FDA's Office of Orphan Products Development, recognizing the apparent usefulness of trientine, began to look for a sponsor. FDA published the information about Wilson's disease and the need for a drug sponsor in the *Federal Register*.

Merck, Sharp & Dohme was already making penicillamine available to doctors to treat about 1,000 patients. Alerted by the notice in the *Federal Register*, the company agreed to develop trientine, even though the potential market for the life-saving drug totaled only 100 patients.

To be sure, trientine had already been discovered by Dr. Walshe. But in 1982 it was still considered an experimental new drug. Under the regulations that guide FDA in enforcing the Federal Food, Drug, and Cosmetic Act, the most costly and time-consuming research and development work is conducted after a drug is given investigational new drug (IND) status, meaning it can be tested in people. It is this work that eats up most of the research funds spent by the sponsor in order to obtain data demonstrating safety and effectiveness. Once approved by FDA as safe and effective, a drug can be made available for general use.

For orphan drugs, development costs are much lower than average since the patient population is so small. Nevertheless, by the early 1980s, there was growing recognition that the government had to assume more of the burden if patients suffering from many rare diseases were to be helped. FDA, acting on behalf of the Department of Health and Human Services, and Congress cooperated to make assistance from the federal government available.

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The Orphan Drug Act cosponsored by Senator Orrin Hatch, R-Utah, and Congressman Waxman and passed by both houses of Congress with bipartisan support, was signed into law by President Reagan on Jan. 4, 1983.

The act fostered the development of orphan drugs by several important means. Under its terms:

- The orphan drug developer has seven years of exclusive use or license, during which no one else may market the drug in the United States unless permitted by the sponsor.
- The developer of an orphan drug may claim up to 63 percent of the cost of clinical studies as a tax credit.
- FDA can assist sponsors of orphan drugs in developing the protocol, or guidelines, for conducting clinical studies.
- FDA can modify certain drug approval requirements for specific orphan drugs. For example, because orphan drugs are used by so few patients, FDA may permit an orphan drug to be tested in a relatively small group of persons. Or, in exceptional cases, FDA can waive the sponsor's need to rule out a drug's long-term potential to produce cancer, reasoning that if left untreated the rare disease victim would have died before cancer could have been induced by the drug.
- FDA can put orphan drugs on a "fast track," giving them high priority for review.
- FDA can make grants of \$20,000 to \$70,000 in support of a sponsor's clinical research of an orphan drug. In fiscal year 1987, FDA had \$3.5 million available to make such grants, and for 1988, \$4 million has been requested.

A 1984 amendment to the 1983 act extends the definition of a rare or orphan drug to products that may be needed by more than 200,000 persons, but have no reasonable prospect of recovering research and development costs from sales in the United States.

How successful has the Orphan Drug Act been? In November 1985, when trientine was approved by FDA, there were 72 designated orphan drugs either approved or under development. In April 1987, FDA's Office of Orphan Products Development designated its 100th orphan drug, 24,25-dihydroxycholecalciferol (DHCC or 24,25D), a compound to treat patients with kidney disease caused by complications from dialysis.

Examples of orphan drugs include:

- **Pentamidine isethionate**, to treat *Pneumocystis carinii* pneumonia, an opportunistic infection that strikes many AIDS patients,
- **Digoxin-specific antibody fragments**, an antidote for life-threatening overdoses of digoxin—a commonly prescribed heart drug,
- **Clofazimine**, an agent to treat a drug-resistant form of Hansen's disease (leprosy),
- **Alpha fetoprotein**, the first standardized diagnostic test to evaluate results of therapies for cancer of the testicles, and thereby help manage treatment,
- **Naltrexone**, to treat narcotic addiction,
- **Cyclosporine**, an immune suppressant to prevent organ transplant rejection,
- **Desmopressin**, a drug to treat moderate hemophilia, and
- **Etoposide**, to treat testicular cancer.

The list of drugs designated as orphans grows year by year. Persons seeking information on rare diseases and therapies to treat them can call the National Organization for Rare Disorders at (203) 746-6518. ■

Egon Weck, a free-lance writer, has written extensively on health and medical issues.

Reducing the Need for Animal Testing

by Richard C. Thompson



One of the biggest controversies in scientific research today centers on the ethics of using animals to test the safety or effectiveness of new products and procedures.

This issue is a matter of great concern to FDA, since the agency regulates a broad range of products — from cosmetics to drugs to food additives — that routinely undergo animal testing by manufacturers before they can be used by people.

FDA's position on animal testing is straightforward and consistent: The use of animal tests by industry to establish the safety of regulated products is necessary to minimize the risks from such products to humans.

FDA regulations on the care of test animals are part of the agency's good laboratory practices and apply to any firm, facility or organization that submits laboratory data to FDA.

Following these regulations means "doing it right the first time." This leads to a reduction in total animal testing and in tests that have to be repeated because the original studies did not establish the safety of the products.

Failure to follow the regulations means that test results may be faulty, the data may be rejected, and whatever the submitter was seeking will be denied.

The regulations call for humane treatment of the animals, with close attention to

housing, bedding, food and water. They stress that animals must be carefully identified and that identity maintained, since losing track of test animals can void a study. Animals from one study must not be mingled with others, and no more animals than are needed are to be used.

NEW AND BETTER WAYS

One of the oldest and formerly most used tests is the LD-50, a test to determine the lethal dose of a chemical for 50 percent of the test animals. In this acute, short-term test, a group of animals (usually rats or mice) is exposed to a single substance. A range of measured doses is given to as many as 100 animals. LD-50 is the dose at which half the test animals can be expected to die. The LD-50 test is used in many industries to screen substances for their relative toxicity and their mode of toxic action. It is mistakenly thought that FDA requires use of LD-50 to establish levels of toxicity. Not so. The agency accepts the results of LD-50 as it would any other test that provides the needed data.

Many scientists and animal welfare advocates are increasingly critical of LD-50, and other tests are now in use that provide similar information with as few as 10 animals.

Another criticized test is the Draize eye

irritant test. This involves placing a substance in the eyes of four to six rabbits and evaluating the effect. The results are used to develop cautionary labeling for products such as soaps and shampoos that — in normal use — might come in contact with and affect the human eye.

However, a new test, developed at the Medical College of Pennsylvania, uses the membrane of a chick embryo to get essentially the same results.

Beyond favoring the embryo test, some scientists suggest that testing might be eliminated entirely for substances that — by their nature — are known to be caustic or irritants.

Although laws and regulations may not actually specify animal testing, they do require that the "best available means for determining safety" be used. Historically that has meant testing with animals. Therefore, alternatives to animal testing are not likely to be widely used until they can be shown to be at least as valid and reliable as the tests they are replacing.

THE "DOGNAPPING LAW"

FDA's regulations are a restatement of the Animal Welfare Act of 1966. When that law was being passed by Congress, it was known as the "dognapping law." This was no attempt at heavy humor. Instead, it



This lifelike model—the “Resusci-dog”—was developed by Dr. Charles Short of Cornell University’s School of Veterinary Medicine and is widely used in veterinary and medical schools to teach the techniques of cardiopulmonary resuscitation (CPR). The Resusci-dog’s “lungs” can be inflated and “blood pressure” and “respiration” maintained, with indicator lights showing that the procedure is being done properly. Such research and teaching aids can reduce the need for live laboratory animals (and, in the long run, are much less expensive).

showed public anger at the tactics of unscrupulous dealers in all parts of the United States who were obtaining and selling animals—generally dogs and cats—for research purposes.

Equipped with leashes, poles, beat-up vans, and very little conscience, these dealers were operating throughout the country. They cared nothing for the condition of the animals when they got them nor while they had them; the quicker they could peddle them, the better. Although states and localities did have laws, how could these animals be traced? It was agreed that federal authority was needed, and the “dognapping law” was enacted.

That 1966 law made the U.S. Department of Agriculture responsible for the “humane care and handling” of six species of animals used in biomedical research: dogs, cats, rabbits, guinea pigs, hamsters, and primates such as monkeys and chimpanzees.

Under the law, persons *supplying* these animals for research purposes must be licensed by USDA and keep records showing where they got their animals and who they sold them to. Facilities *using* the animals report annually on the six species.

PROTECTION IS WIDENED

The act has been amended several times: in 1970 to include other warm-blooded animals; in 1976 to regulate the transport of animals by commercial carriers and by intermediate handlers; and in 1985 to require animal care committees at using facilities. The latter are much like the review boards for human subjects (see “Protecting Human Guinea Pigs,” *FDA Consumer*, December 1986–January 1987).

The Animal Welfare Act is administered by USDA’s Animal and Plant Health Inspection Service through five regional offices. A USDA veterinarian is in charge in each state, and veterinarians also are assigned to various locations in each state. There are some 300 veterinarians whose duties include making unannounced inspections of some 1,200 animal users and suppliers nationwide.

The law sets standards for animal handling, housing, feeding, watering, sanitation, ventilation, shelter from extremes of temperature and weather, transportation, and veterinary care. Facilities can expect an average of two inspections a year, although those with good inspection histo-

ries might be checked only once a year, and those with problems could be checked every month or so until the problems are resolved.

As of 1985, there were in the United States some 500 research facilities fully accredited by the American Association for Laboratory Animal Care and another 500 partially accredited. This includes universities and hospitals; medical, dental and veterinary schools; colleges of pharmacy, arts, engineering and biological science; pharmaceutical manufacturers and commercial laboratories; government agencies and labs; Veterans Administration medical centers; and laboratory animal breeders.

Estimates vary as to the number of research animals used in the United States, but data suggests about 20 million were used for research and testing in 1983, the last full report year. Some 15 million of these were rats and mice. Almost 1.8 million were the six identified species (dogs, cats, hamsters, rabbits, guinea pigs, and primates) for which reporting figures are most accurate.

Although government agencies do not necessarily do the tests, the federal government is responsible for much of the animal testing that is done.

EPA IS BIGGEST DATA USER

With its need to establish the safety of pesticides, the Environmental Protection Agency generates the largest volume of animal test information. Before a pesticide can be marketed, manufacturers must show EPA that the product is safe and can be safely applied. For substances other than pesticides, EPA relies largely on testing that it sponsors and on the scientific literature.

The Food and Drug Administration—well below EPA in its use of animal data—requires that manufacturers obtain evidence in the earliest stages of product development showing that the drug or device they intend to market is safe. This has traditionally been done through tests using laboratory animals.

Other agencies that depend on animal test data include the Consumer Product Safety Commission, Occupational Safety and Health Administration, Department of Transportation, Department of Agriculture, National Institute of Environmental Health Sciences, Federal Trade Commission, and the Centers for Disease Control.

CONGRESSIONAL OFFICE SEES "MIDDLE GROUND"

The Office of Technology Assessment (OTA)—a science staff advisory to Congress—reported in 1986 that debate over the use of animals in testing and research “has been taken up by proponents holding a wide spectrum of views.” These range from abolishing animal use for moral and ethical reasons to belief in free rein in the use of animals.

OTA feels that many groups are now taking a middle ground and that it is misleading to characterize organizations as being either pro-animal or pro-research.

Standing on that middle ground, OTA sees alternatives to animal use as a matter of replacement, reduction and refinement.

Replacement means using methods that do not require animals in place of those that do. Veterinary students, for example, might use a canine cardiopulmonary resuscitation simulator (the “Resusci-Dog” photo with this article) instead of living, anesthetized dogs. The horseshoe crab is increasingly accepted as a substitute for rabbits in testing for the fever effects of drugs.

Cells show a variety of reactions to toxins, including cell death, changes in metabolic activity, and damage to genetic materials. On this basis, human cell cultures obtained in surgery or from cadavers might replace mice and rats in product testing. Animal cells and microorganisms could also be used in this way.

OTA doubts that animals can be totally replaced with non-animal methods in most areas of research and experimentation. Research will continue to require intact, live animals for observing complex interactions of cells, tissues and organs.

Reduction refers to the use of fewer animals. Reducing the number of test animals can be done by using no more than are actually needed for the test; by combining tests in such a way that fewer animals are used; and by retrieving, storing and exchanging test data so that earlier known work is not duplicated.

Changing their test practices might allow scientists to estimate the lethal dose of a chemical or other substance using far fewer animals than are needed at present. Careful design of experiments with attention to statistical findings—a more closely controlled study—could lead to decreases in the number of animals that must be used.

Refinement means that animals that are used are subjected to less pain, discomfort and distress. This may require administration of anesthetics and tranquilizers; carefully watching behavior for signs of pain or distress and giving anesthesia or stopping the procedure; and making use of visual imaging technology instead of invasive surgical procedures.

As alternative methods are developed, a computerized registry of information would encourage their adoption. Such a system was offered in the 1970s as a Laboratory Animal Data Bank, but closed down because of too few users. However, this was before the era of computer networking and personal computers.

The National Library of Medicine presently has “animal testing alternatives” as a catalog and data base heading that is used by scientists throughout the world to find reference books and other sources on the subject. The National Agricultural Library was told by Congress in 1985 to offer an information service on improvements in animal experimentation that could lead to reduced use.

PUBLIC SUPPORTS RESEARCH AND TESTING

Former Florida Congressman Paul Rogers, speaking for the Foundation for Biomedical Research, said in 1986 that his organization has two chief concerns: that progress in biomedical research continue unimpeded; and that research adhere to the highest standards for the care and use of animals needed in scientific research.

According to Rogers, a poll commissioned by the foundation showed that:

- Seventy-seven percent of the American people endorse the use of animals in place of humans in the study of biological functions and diseases.
- Seventy percent agree that some research with animals is necessary, even when it may not lead directly to a treatment or cure of a specific disease.
- A majority support the use of animals in safety testing of drugs, medical and surgical devices, insecticides and pesticides, and skin-care products and cosmetics.

The poll indicates that the public generally accepts the use of animals in medical studies and research and in the testing of products before they are marketed. ■

Richard C. Thompson is a member of FDA's public affairs staff.

Artificial Fingernails: Apply with Caution

by Annabel Hecht

The art teacher's nails were, admittedly, in bad shape. The materials she used in her classes—clay, finger paints, India ink—plus the constant hand washing to get them off had made her nails split and break. Usually she just lived with it, but the following week she was getting married and naturally wanted her nails to look their best. Thanks to a procedure that has become increasingly popular coast to coast, she was able to do that with little trouble. She had new nails sculptured over the old.

Today, modern acrylics and other plastic materials make it possible to “grow” a whole new set of nails in a matter of minutes or to have perfect nails to mask those that are broken, chewed to the quick, or just not as long as you would like. Some of these artificial nails can be had only at beauty salons or at ultra-specialized nail salons; others are do-it-yourself. But, whatever the type, it's important to know that these products are not without risk. Used improperly, they can cause infections, allergic reactions, and other problems. So care in creating and tending your new nails will help make sure the attention they bring you isn't just from your dermatologist.

To create the art teacher's new nails, the nail salon technician first buffed each nail to remove natural oils and slightly roughen the surface so the acrylic material would adhere. Then she applied an antiseptic as a precaution against infection. Finally, to support the sculptured extension and to protect the surrounding skin, she fitted a small horseshoe-shaped collar made of foil with a mylar coating around each nail.

Using a vibrating brush first dipped in a clear liquid, then in a powder, the technician placed a bead of the resulting material on the nail. The vibrations of the brush helped blend the material and spread it evenly over the nail. Additional material was added to build and extend the new nail. The technician had to work quickly because the acrylic material hardens fast, and in less than half an hour the teacher's new nails were finished, ready to be further shaped and polished.

That's not quite the end of the process, however. The sculptured

nail will move up as the nail grows, leaving a space at the cuticle end of the nail. In order to maintain her new nails the art teacher will have to return every two or three weeks for a “fill-in.” Once applied, the artificial nails can stay on for years. However, Dr. Richard Sher, a dermatologist and expert on nails formerly with Brown University in Rhode Island, says he advises his patients to remove the acrylic at least once a year to give the nails a rest.

Techniques used to apply sculptured nails may vary from salon to salon, but the materials used are basically the same and are, incidentally, from the same class of chemicals as those used to make dentures—the pink-colored base that holds the false teeth, not the teeth themselves. (When used in dentistry these chemicals are regulated as medical devices by FDA. However, the agency does not have authority to require approval of these same chemicals for use in cosmetics.)

The powder is usually polymethyl methacrylate with benzoyl peroxide added as a catalyst; the liquid is a mixture of one or more methacrylate ester monomers and a promoter such as N,N-dimethyl-p-toluidine. When combined, the chemicals react so that the monomer (a simple molecule) becomes a polymer—a compound made up of two or more monomers. This is called polymerization.

Some nail-building products are gels that usually contain methacrylic or acrylic ester monomers, polyurethane, and a curing agent all in one. They are painted on the nails in much the same way as the two-part process, but are then “cured,” or hardened, under visible or ultraviolet light or by an activator in the form of a spray.

Longer nails can also be created by attaching plastic tips to the natural nail with a special acrylic glue. About one-fourth to one-half of the nail will be covered, depending on the design of the tip. In the case of nail biters, who have less to start with, the tip may cover a good part of the nail. Acrylic nail builders and nail wrappings may be applied over the tip and the nail to strengthen the bond between the two.



Press-on and glue-on, do-it-yourself plastic nails pose few hazards if used according to the package directions.

Nail wraps also may be used alone to strengthen and repair natural nails without artificial tips. The wraps, which are made of paper, silk, linen, fiberglass, or—for those with exotic tastes—reptile skins, are applied with nail glue or sealers, and can be filed or polished. Like the sculptured nails, nail tips and wraps move up as the nails grow, necessitating return visits for fill-ins and fix-ups.

What must be the ultimate in artificial finger adornment is the 14-karat gold nail. Often sold in jewelry stores, gold nails are available plain or set with diamonds and are applied in the same way as plastic nails.

For the consumer who wants longer nails but can't afford salon prices (a new set of nails may run \$50 or more), satisfaction is as close as the nearest drugstore.

Most stores carry a selection of do-it-yourself nail extenders. For those who want sculptured nails there is a kit containing the acrylic liquid and powder, nail forms, and brushes similar to those used in nail salons. Also available are the preformed plastic tips and full nails that can be had in "natural," "European," "glamour" or "Dragon Lady" lengths. Plastic nails are either glued on with an acrylic substance or pressed on using a patch with adhesive on both sides. Some of the plastic nails come already colored; others are clear or white and can be polished like a natural nail.

While all of these products—from store or salon—can pose some hazards, today's materials are not likely to cause problems as did those used when artificial nails first became available. In the early 1970s, FDA received complaints of discoloration, deformity or loss of fingernails, and irritation and inflammation of the nail bed or nail fold at the base of the nail from women who had used nail-building kits containing methyl methacrylate.

FDA subsequently sued C.E.B. Products, Inc., the manufacturer of a methyl methacrylate monomer-containing nail product called Long Nails, for distributing an adulterated cosmetic in interstate commerce. Distribution of Long Nails was halted under

a court order. This action, and the seizure and recall of other similar products during the second half of 1974 and in 1975, led manufacturers to reformulate their products. Methyl methacrylate was replaced by other methacrylate esters such as ethyl methacrylate, isobutyl methacrylate, and many other chemically related monomers.

Reformulation, however, did not completely eliminate problems with artificial nails. From 1976 to 1986, FDA received 65 consumer complaints about nail-building products, including nail damage, skin reactions, infections, headaches, sneezing, nausea and coughing. This does not represent all of the adverse reactions that may have occurred during this period, however. FDA receives relatively few cosmetic-related consumer complaints, and manufacturers are not required to pass along any complaints they receive.

Some people who are sensitive to acrylics have had allergic reactions to sculptured nails. The chemicals may cause redness, swelling and pain in the nail bed and the surrounding tissue. Heinz Eiermann, director of the division of colors and cosmetics in FDA's Center for Food Safety and Applied Nutrition, says these reactions may occur when the methacrylate monomers are not completely cured, or polymerized, leaving some monomer free to enter the natural nail. In some cases, the reaction is so severe that the natural nail separates from the nail bed, and, although a new nail usually grows back, it may be imperfect if the nail root has been damaged.

Once a person becomes allergic to acrylics—which can happen after repeated exposure to them—she (or he) may never be able to use the products again. (For more on sensitization, see "Cosmetic Allergies" in the November 1986 *FDA Consumer*.) But allergic reactions to acrylic nails are infrequent, Eiermann says. Of greater concern, perhaps, are bacterial or fungal infections that develop on top of the natural nail between it and the artificial nail.

(Continued on page 21)

The Nail File: All the Facts at Your Fingertips

Marvelous things, fingernails. They protect the ends of the fingers, help make fingertips more sensitive to touch, provide a handy device for scratching, and, in emergencies, double as letter openers, staple removers, and even tiny screwdrivers. In addition to their functional aspects, fingernails can become objects of adornment, taking on whatever color or decoration (including precious metal and gemstones) suits the occasion.

Human nails, like human hair, are made up of a tough protein called keratin. The nail plate on top of the finger is formed from the nail matrix, a special group of cells under the base of the nail near the cuticle. Part of this matrix is visible on the larger nails as the white moon (lunula) just past the cuticle.

The nail plate is translucent. The pink color of normal nails comes from the blood in the nail bed on which the plate rests. The nail plate is kept on the straight and narrow by folds of skin on the two sides and at its base. Without these folds the nails would grow straight up.

Technically, since it does not contain living cells, the nail plate is not alive. Yet it grows continually at a speed of about 3 millimeters—an eighth of an inch—a month. It takes five to six months to grow a new fingernail. For reasons unknown, the nail on the middle finger grows the fastest, while those on the little finger and the thumb grow the slowest. If nails didn't break from such mundane tasks as dialing telephones, typing and housework, they could conceivably grow as long as . . . well, very long.

(The longest nails on record, according to the 1985 *Guinness Book of Records*, belong to Shridhar Chillal of Poona, India. As of April 1984, the curving nails on his left hand together measured 135 inches—more than 11 feet.)

Pregnancy or an excess of thyroid hormone speeds up nail growth. Psoriasis, a skin disease that speeds the growth of skin cells, also makes nails grow faster. Nails grow faster in warm weather and when they are recovering from an injury.

In contrast, advancing age, cold weather, malnutrition, and illness can slow and even stop nail growth. A tell-tale sign that a person has suffered a serious illness or had major surgery is a thin groove from side to side across the nail plate, called a "beau's line," after a 19th

century French physician. The position on the nail is a clue to when the illness occurred.

Nails provide other indications that their owner is or has been ill. For instance, an opaque or white nail could signal cirrhosis of the liver; a nail that is red at the tip but white across the base could indicate chronic kidney disease. Besides making the nails grow faster, psoriasis may cause yellowing and little round pits in the nail plate. It also may cause the nail to separate from the nail bed, as will an overactive thyroid.

Vertical ridges—from base to tip—may be a sign of Raynaud's disease (a circulatory disorder), rheumatoid arthritis, or lichen planus, an inflammatory skin disease.

Brittle nails may result from age, anemia or poor circulation, but the most common culprit is water. Nails are never as tough as they look; in fact they are actually permeable—water and solvents can pass through them. When they are immersed in water the nails swell; out of water they dry out and shrink. Frequent swelling and shrinking damages the structure of the nail, causing it to break easily.

Changes in nails can occur when an individual is exposed to chemicals—of the medicinal variety or otherwise. Discoloration and separation of the nails have been reported as unusual side effects of long-term use of tetracycline. Nail changes, including loss of the nail, also have been associated with cancer drugs. An excess of copper or silver in the body turns the nails blue. Too little iron in the system can lead to a spoon-shaped nail—one whose sides curve up instead of down over the finger. Arsenic, which has a particular attraction to keratin, can be detected by white bands on the nails.

Some chemicals used in agriculture—paraquat, diquat and dinitro-ortho-cresol—have caused loosening and discoloration of nails in persons exposed to these substances.

Nail polishes, used to beautify and protect the nails, may also produce some unpleasant side effects, such as brittle nails and allergic reactions involving the nails themselves, as well as other parts of the body touched by the polished nail. FDA requires that the ingredients in nail polishes and other cosmetics be listed on the product label so that consumers can

avoid ingredients that cause them problems.

Some nail abnormalities result from injury, such as pressure put on the nail plate during a manicure or a misdirected hammer blow. Nails are also subject to their own diseases, principally ringworm (a type of fungal infection) and warts.

Characteristic symptoms of ringworm of the nails, called *tinea unguium*, include green discoloration or yellowing of the ends of the nails and nail folds and a lifting of the nail plate. Because these symptoms are also associated with psoriasis, an accurate diagnosis is important.

The prescription drug griseofulvin (trade names Fulvicin, Grifulvin V and Grisactin) is the cornerstone for treatment of ringworm, but full recovery takes four to six months. Over-the-counter drugs containing anti-fungal ingredients are not usually effective in treating this nail disorder.

Warts are hard to treat for a number of reasons. For instance, they may exist in apparently healthy tissue surrounding the nail or extend far below the surface. The patient with many warts is probably a nail biter whose nibbling spreads the infection.

Freezing with liquid nitrogen is a common treatment for warts around the nails. Others are topical cantharidin (a prescription drug) or salicylic acid (an over-the-counter product). Surgery is sometimes necessary, but it can be tricky because of the danger of distorting the nail structure.

While some insults to the nails can't always be avoided, many can be prevented by common-sense nail care. For instance, wearing protective gloves while doing household and gardening chores will prevent overexposure to water, harsh chemicals, and microorganisms that live in the soil. Nails should be kept neatly manicured, using cosmetics judiciously. Nail polish should not be removed too often, as some polish removers may be harsh and can dry and irritate the nails. It is best to keep polish on for five or six days, then remove it, and wait a day or two to reapply.

While malnutrition may have an effect on nails—anorexics have brittle hair and nails—experts agree that there is no magic diet to improve them. Some years ago many women fell prey to the myth that eating plain gelatin would give them beautiful nails. There is no scientific evidence that it does.

The best advice is to eat a well-balanced diet to maintain optimum overall health. Then the nails will take care of themselves. ■



Never apply an artificial nail if the nail or tissue around it is infected or irritated.

(Continued from page 19)

A bump or knock to a long artificial nail may cause it to lift from the natural nail at the base, leaving an opening for dirt to get in. If the nail is reglued without proper cleaning, bacterial or fungal spores may grow between the nails and possibly spread into the natural nail.

The primary symptom of a fungal infection is blue-green discoloration of the nail—an indication that the fungus has grown into the nail plate. In mild cases there is no pain. When discoloration is noticed, all artificial coloring must be removed before the infected areas can be treated with an antimicrobial product. Unfortunately, the discoloration will remain four to six months until the nails have grown out. Severe, painful cases of infection should be treated by a dermatologist.

The press-on and glue-on, do-it-yourself plastic nails pose few hazards if used according to the package directions. But if care isn't taken, glue can bond to the skin or irritate the eye. Some products warn that their adhesives are flammable and should be used in a well-ventilated area. The plastic nails themselves should be kept away from heat and flames. Full-sized nails should be removed after 48 hours, in part because these nails do not always fit tightly over the natural nail, allowing space for microbial contamination.

Besides the instructions, the artificial nail package includes another very important item—the ingredient list. Unlike drugs, cosmetics—including artificial fingernails—do not have to be approved for safety and effectiveness by FDA before they go on the market, says John Wenninger, associate director for cosmetics of FDA's colors and cosmetics division. But the law does require manufacturers to tell what's in cosmetics sold for use at home. (Ingredient labeling is not required on products sold solely for use in nail and beauty salons.) Ingredient information can be very helpful in alerting consumers to chemicals that could cause allergic reactions or other problems, says Wenninger. And if a problem requiring medical attention should develop, the physi-

cian will be aided by knowing what chemicals the patient was exposed to.

FDA continues to monitor consumer complaints of adverse reactions to all types of artificial nails and will take appropriate regulatory action against products that pose a health hazard. Agency laboratories are also analyzing nail products used in beauty and nail salons to get a better understanding of what chemicals are in them. The law does not require cosmetic products to be registered with FDA, although some firms do register their formulas voluntarily. However, very few, if any, nail-extender products used in salons are registered.

Here are some things consumers should bear in mind if they intend to use artificial nails:

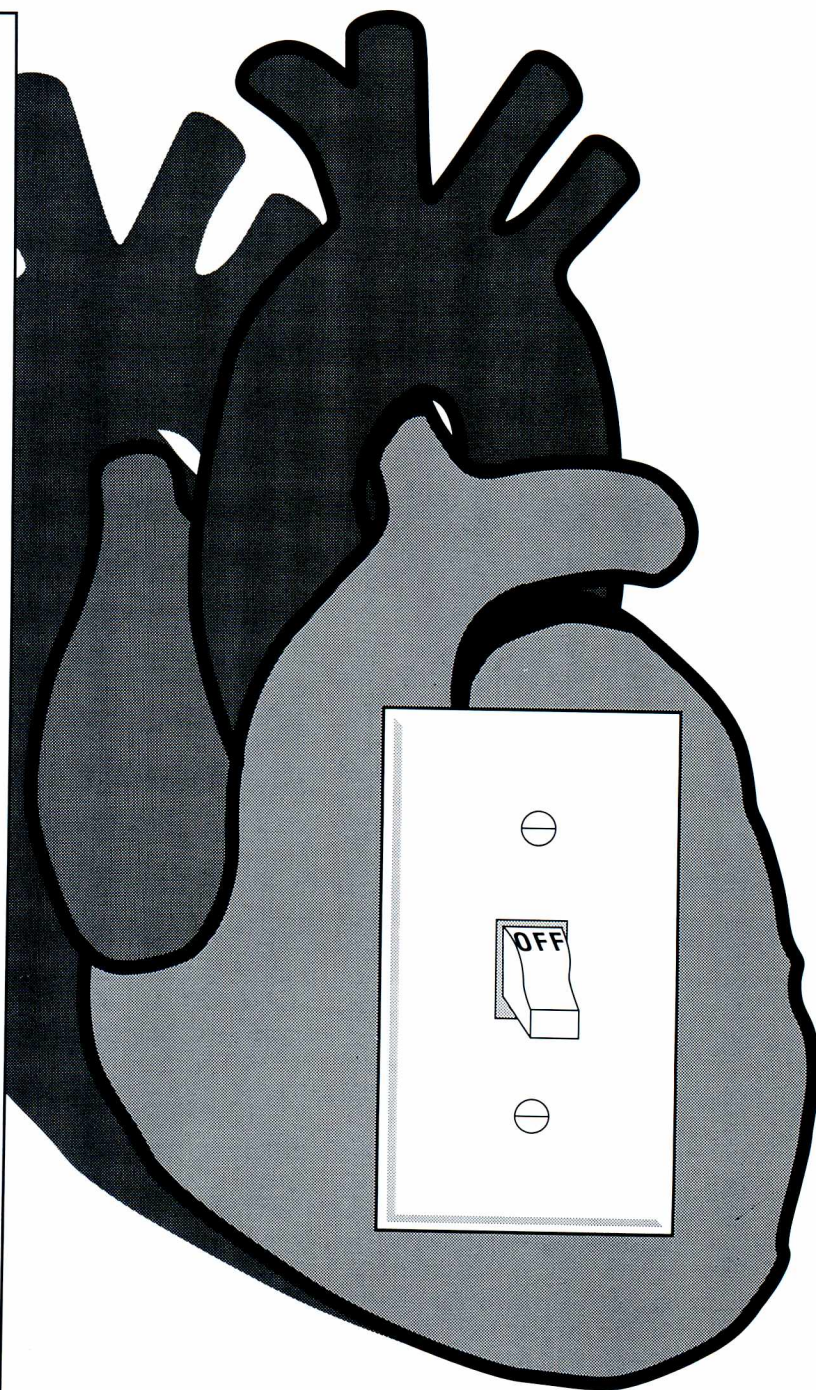
- If there is any question about sensitivity to the materials in sculptured nails, have one nail done as a test and wait a few days to see if any reaction develops.
- Never apply an artificial nail if the nail or tissue around it is infected or irritated; let the infection heal first.
- Read instructions for do-it-yourself nails before applying them, and follow the directions carefully. Save the ingredient list for your doctor in case of an allergic reaction or other injury.
- Treat your artificial nails with care. They may look—and be—stronger than your own, but they can still break and separate. Protect them from harsh detergents and microbial contamination. Try not to bump or knock the tips. Find new ways to do ordinary tasks, like using a pencil to dial the phone.
- If an artificial nail separates, dip the fingertip into rubbing alcohol to clean the space between the natural and artificial nails before reattaching the artificial nail. This will help prevent infection. Never use household glues for home repairs. Use only products intended for such use, and follow the instructions and heed all cautions on the product label. ■

Annabel Hecht is a free-lance writer in Silver Spring, Md., specializing in health reporting.

Clot-Busting Drugs by Catherine Carey

To Turn Off Heart Attacks

Every year, about 1.5 million Americans suffer a heart attack. Of that number, one-third die within one year, 100,000 before they can be hospitalized. Typically, a blood clot develops in one of the arteries to the heart, preventing oxygen-rich blood from that part of the heart muscle. The greater the blockage and the longer it continues, the more of the heart muscle that is lost. Substantial loss of heart muscle can lead to heart failure and death.



But over the past several years, researchers have developed drugs called thrombolytic agents that can help dissolve the clots. Blood can then again flow through the artery, preventing further damage to the heart. Last fall, FDA approved alteplase (trade name Activase), one of a new class of thrombolytic agents known as tissue plasminogen activators (TPA). In addition, FDA approved the expanded use of another thrombolytic agent, streptokinase (trade names Kabikinase and Streptase). These approvals mean that heart attack victims have greater reason for hope than ever before that they will successfully recover from their attacks.

Alteplase is a genetically engineered copy of a protein produced naturally by the body. In 1979, scientists in Belgium first

been tested in more than 4,000 patients. It has been shown in controlled clinical trials to dissolve clots in 71 percent of heart attack patients when injected within six hours after symptoms occur. In separate trials, the drug significantly improved heart function when given within four hours.

One of the largest studies, sponsored by the National Heart, Lung, and Blood Institute, was known as the Thrombolysis in Myocardial Infarction Trial. This study included alteplase and streptokinase. Streptokinase — made by Behringwerke AG, a German firm represented in the United States by Hoechst-Roussel Pharmaceuticals Inc. of Somerville, N.J., and KabiVitrum AB of Stockholm, Sweden, which has offices in Alameda, Calif. — has been licensed for use in treating heart

percent reduction in mortality,” said FDA Commissioner Frank E. Young, M.D., Ph.D., “was observed when streptokinase was administered within one hour of the onset of symptoms.” In separate studies, it was shown to improve heart function.

Alteplase and streptokinase can be used to treat the vast majority of heart attack victims, but should not be given to patients at high risk of hemorrhaging. This includes patients with internal bleeding; a recent stroke, surgery or major injury; long-standing, uncontrolled high blood pressure; or a bleeding disorder. Both drugs also should be used with caution in people over 75, in pregnant women, and where bleeding is a significant hazard.

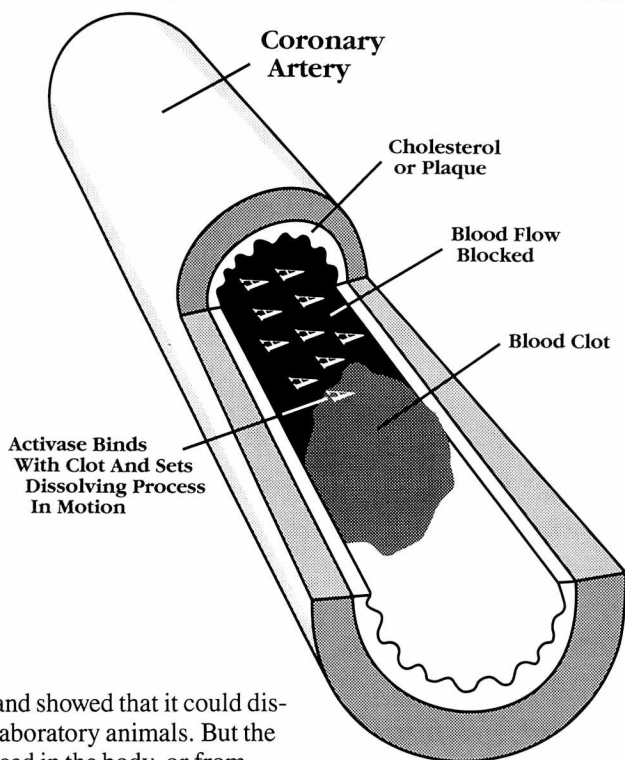
Bleeding within the brain was one of several issues that concerned the Cardiovascular and Renal Drugs Advisory Committee — an advisory committee made up of nongovernment experts — on May 29, 1987. This committee advised FDA to obtain more data on safety and effectiveness before approving alteplase.

Data submitted later showed that the bleeding problem occurred more frequently at higher doses, but at the recommended dose of 100 milligrams it occurred only in 0.4 percent of patients. Bleeding occurred at about the same rate with streptokinase when given at recommended dosages.

The committee also recommended FDA find out whether a change in manufacturing procedures at Genentech made any difference in alteplase’s safety and effectiveness. Data submitted by the manufacturer showed that it did not. In addition, the committee questioned whether alteplase’s ability to dissolve clots actually, as theorized, limited heart damage. Subsequent data showed that it did.

Robert E. Windom, M.D., assistant secretary for health, observed that although changes in diet, anti-smoking campaigns, and other factors have helped reduce deaths from heart disease, coronary heart disease “remains America’s number one killer, responsible for about 768,000 deaths each year — or about a third of all deaths,” he said. “At some point in their lives,” Dr. Windom added, “one out of every four or five people will feel the pain and constriction of a heart attack — pressure or pain in their chest or pain in their left arm.” When that happens, he advised, “Don’t waste time hoping against hope that the pain will go away . . . get help quickly.” ■

Catherine Carey is a member of FDA’s public affairs staff.



purified TPA and showed that it could dissolve clots in laboratory animals. But the amount produced in the body, or from most human cells in culture, is so minute that large-scale production would be impractical. So, in 1981, Genentech Inc., of South San Francisco, Calif., began using recombinant DNA technology to produce enough alteplase to be tested in heart attack victims.

Genetically engineered alteplase is made by introducing the human gene that holds the instructions for producing the protein into cells originally derived from the ovaries of Chinese hamsters. The inserted gene programs the cells to consistently produce large quantities of alteplase.

Clinical trials of alteplase began in 1984. In all, Genentech’s alteplase has

attacks since 1982. Until last fall, however, the use of streptokinase, which is derived from *Streptococci* bacteria, was limited because it could be administered only by inserting a catheter directly into the coronary artery. This procedure could only be done in hospitals that have special coronary care units.

But recent data from clinical trials, including one involving more than 11,000 patients, have shown that streptokinase given intravenously — by a needle inserted into a vein — reduces the death rate among recipients by 20 percent to 25 percent when given within six hours after a heart attack. “The most dramatic result — a 47

Quackery Targets Teens



Quackery, an age-old business, costs Americans billions of dollars each year and immeasurable losses suffered from harmful products and delayed medical treatment. The quack's victims are usually thought of as the aged or chronically ill.

But quacks are quick to spot new markets, so it's not surprising that they have discovered teenagers. These youths and their impatience with the blossoming process are fertile ground for quacks. Teenagers are ready to experiment with products that promise to speed their development and ease growing pains.

And many of these junior and senior high school age children have money enough to do the experimenting. In fact, a study by Teenage Research Unlimited revealed that 29 million teenagers spent an average of \$80 a month on personal items in 1985 for a total of nearly \$28 billion.

Teenagers, anxious to speed their development, are fertile ground for quacks.

Further, in families in which both parents work, teens take on more of the family shopping responsibilities. The U.S. Labor Department reports that as of March 1986, 65 percent of families with teenagers had two working parents. And a 1987 report by Teen Research Unlimited showed that teens do the shopping in 70 percent of households with working mothers.

These young shoppers often have access to mom or pop's credit card. And, like their parents, they are buying more

through the mail, a medium that offers a cloak of anonymity under which quacks thrive.

The teen years are often insecure years, filled with questions like: "Am I beautiful (or handsome)?" "Will my breasts ever develop?" "Shouldn't I be more muscular?" "Am I too fat?" "Would a tan give me more sex appeal?"

Quacks love such questions. And they're ready with answers that have been—according to them—"overlooked or ignored by the established scientific community."

Time is of such essence to the young that they grasp at straws and don't recognize the quack's deceptions for what they really are.

Take a look at some of the advertisements in teen magazines. There's a "space age diet" that allows you to "eat all day and still lose weight," a beauty cream that

There is no device or system of exercise that will increase the size of the breasts.

will ensure "gorgeous, proportioned breasts," and a pill to provide a tan overnight. Sound unlikely? Impossible is a better word. But, fond of superlatives and driven by desire, teenagers are ready to believe such ads.

Here are some of the dubious products that teenagers today are asked to believe in:

BREAST DEVELOPERS

For decades, millions of dollars have been spent on devices, creams and lotions advertised as breast developers. All wasted. There is no device or system of exercise that will increase the size of the breasts. At best, devices promoted as breast developers merely strengthen and develop the muscles that support the breasts, and exercising these muscles will not appreciably increase breast size.

Creams and lotions advertised as breast developers don't work either. Some contain the hormone estrogen. Estrogen can increase breast size, but in order to be sold without a prescription these products must contain such a small amount of the hormone that its effect is insignificant. (Estrogen is used in birth control pills and to treat symptoms of menopause. FDA approval for estrogen does not include use for breast development.)

The only proven method of increasing breast size is breast augmentation surgery, which carries some risks and is hardly recommended for teenagers.

WEIGHT LOSS

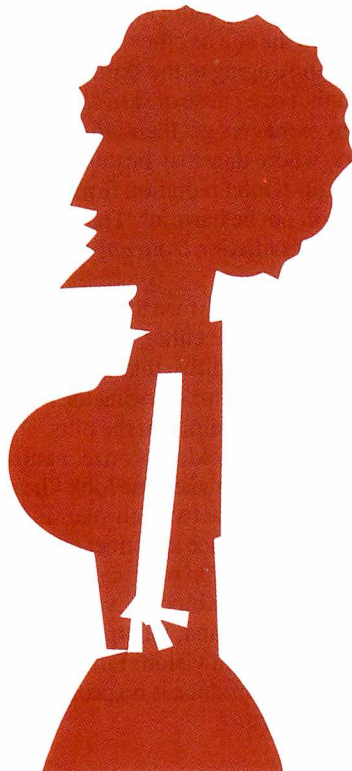
Teenagers—especially girls—are not exempt from the American penchant for dieting. One expert says that as many as three-fourths of high school girls are on a diet at any one time. Writing in the May-June 1987 issue of *Nutrition Today*, Dr.

Kelly Brownell of the University of Pennsylvania School of Medicine said that some children begin dieting as early as the fourth grade.

Those figures may startle some people, but not the quacks. They know them well and have pounced on that audience, offering "magical" diets and pills to keep the pounds off. Most of the diets and virtually all of the pills are worthless; some are even dangerous. At times, some diets will achieve a temporary weight loss that is usually unrelated to the "magical" food or pill.

The dieting craze may be particularly questionable for adolescents, since a well-balanced diet is vital during the teen years when the body goes through dramatic change and growth.

Depending on the ingredients, some pills promoted for weight loss can cause side effects such as nervousness, nausea and insomnia, and can also be addictive.



One expert says that as many as three-fourths of high school girls are on a diet at any one time.

The recognized active ingredient in most nonprescription diet pills is either phenylpropanolamine (PPA) or benzocaine. The effectiveness of these two ingredients for weight loss has yet to be determined by FDA. However, too much PPA has been associated with elevated blood pressure. Benzocaine is supposed to work by numbing the inside of the mouth to make food less appetizing.

Most weight-loss products sold as part of a diet-and-pill plan are harmless. The products don't work, but the plan may. Of course, the plan would work just as well without the product, which is nothing more than a psychological crutch.

Some devices are also promoted for weight loss. Electrical muscle stimulators, for example, have a legitimate use for physical therapy treatment, but FDA has had to take a number of such devices off the market because they were promoted for weight loss and "body toning." These stimulators can be dangerous when used incorrectly. Hazards include electrical shocks and burns.

Body wraps are another favorite gimmick of the quacks. They're touted as a means of "burning fat." The wraps are worn around part or all of the body, sometimes preceded by the application of a cream or lotion. Temporary weight loss may occur as the result of sweating and loss of water in the tissues, but when the water content of the tissue returns to normal, the "lost" weight reappears. The wraps do not "burn" or dissolve fat. Furthermore, experts consider them dangerous because they can cause severe dehydration and circulatory problems.

There are no magic foods, pills, wraps, diets or wands for losing weight. The only way to lose weight is to consistently eat fewer calories than the body needs and uses. But teenagers should be cautioned about excessive dieting. Their growing bodies can't tolerate the nutrient loss that comes with eating too little.

(Continued on next page)

Steroids may well build muscle, but their use can also stunt growth, lead to cancer, ruin the liver, and cause other complications.

(Continued from previous page)

STEROIDS AND GROWTH HORMONE

Quackery. That is the bane of sports medicine. We've rid ourselves of some of the worst but there are still many people handing out get-good-quick pills, touting medicines that send blue sparks and make big muscles, or advising athletes to drink superduper seaweed extracts.

—Dr. Daniel F. Hanley, Bowdoin College, Brunswick, Maine, as quoted in *Death in the Locker Room*.

Our sports-loving nation loves a winner, and it's fair to say that most of the 5 million boys and girls who compete in high school sports love to win. Some of them will go to great lengths to do so. That may mean using performance-enhancing drugs such as anabolic steroids and human growth hormone.

Anabolic steroids—compounds similar to the male hormone testosterone—are too often used by athletes, both boys and girls, to build muscle. They are also used by young men who just want to look better. They are prescription drugs, but most of those who use them obtain them illegally, often from the black market. Steroids have a lot of unwanted side effects—that's why they are supposed to be sold only by prescription. They may well build muscle, but it's a losing proposition, because their use—particularly in the large doses that athletes take—can stunt growth, lead to cancer, ruin the liver, and bring on other complications, including enlarged breasts in boys. For girls, the side effects include developing masculine traits that may be irreversible.

Black-market steroids often are produced in another country or by clandestine domestic manufacturers under questionable conditions and may be contaminated. The quacks have also moved in with "hony steroids and phony pills that they say—falsely—will counter some of the side effects of steroids.

Earlier this year, FDA warned that a counterfeit version of the hormone human chorionic gonadotropin, or HCG, was being sold to weight lifters and other athletes. The bogus hormones were contaminated with a substance that causes infections and fever.

A black market has also sprung up for human growth hormone. This prescription drug is legitimately given to children who suffer from pituitary dwarfism or growth hormone deficiency, but it, too, has dangerous side effects. Nevertheless, athletes seeking to benefit from added growth are buying the hormone on the black market. Quacks are also marketing "growth tablets" that, in fact, contain no hormones or any other ingredients that can promote growth.

TANNING AND TANNING PILLS

Tanning is never harmless, regardless of the source: the sun, a sunlamp, a tanning bed, or a pill. Exposure to ultraviolet radiation from the sun or other sources leads to premature aging of the skin. It is also the number one cause of skin cancer.

Many teenagers get their tans at tanning parlors, where they may be told that the type of ultraviolet radiation from the lamps will not be harmful. That's not true. Ultraviolet radiation from *any* source can be harmful.

Other youths may turn to tanning pills. But they're not safe either. They generally contain a color additive that has not been approved by FDA for coloring the body. Advertisements claim that the pills produce "a rich, golden-bronze, natural-looking tan" that makes one look "healthy, energetic, and attractive" all year. But the pills actually produce a distinct orange tinge on the skin. The pills may also leave fatty deposits in the blood, liver and skin, and on the eye's retina, where they may interfere with night vision. Further, the "tan" the pills produce is no protection against sunburn.

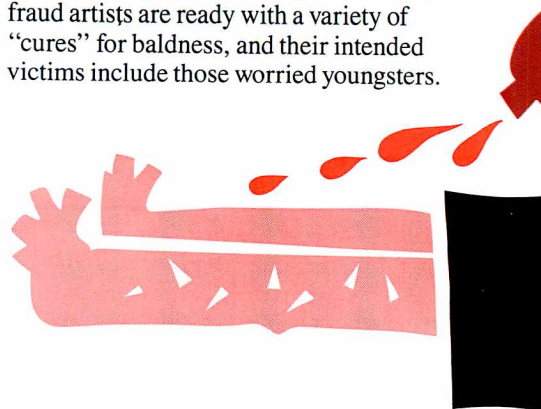
HAIR: REMOVAL AND GROWTH

The only effective way to remove hair permanently is with electrolysis—a process by which hair roots are destroyed with an electrified needle. Electrolysis should only be performed by a physician or professional electrologist, according to the American Medical Association (AMA). While it is safe when done correctly, it can be tedious, painful and expensive, the AMA adds. Scarring may result and regrowth is possible.

Effective means of temporarily removing hair include *shaving*, *tweezing*, *waxing*, and using *cream or lotion* depilatories. But FDA cautions that there is no risk-free method of removing hair. Waxing, for example, can be painful, and creams can cause rashes and swelling.

There is limited good news about removing hair, however. According to the AMA, hair removal does not make renewed growth thicker or stiffer, nor does it quicken regrowth.

While girls struggle to remove hair, some teenage boys worry that they won't be able to keep theirs. Since most baldness is hereditary, young men may take a look at their long-since bald fathers and fear that they will soon be watching the tops of their heads get smoother. There's currently no solution to this dilemma, a fact that bothers quacks not at all. The health fraud artists are ready with a variety of "cures" for baldness, and their intended victims include those worried youngsters.



When taken in excess or mixed with alcohol, "look-alikes" have caused strokes and death.

The would-be hair restorers are trafficking these days in a drug that has shown some ability to stimulate hair growth. That drug is minoxidil, which is used to treat high blood pressure. Publicity about the prescription drug's link to hair growth has laid just enough groundwork for the quacks to capitalize on. However, minoxidil has yet to be approved by FDA for growing hair. So there remains no product available that will grow hair, despite quack ads to the contrary.

"LOOK-ALIKE" DRUGS

The widespread use of illegal drugs among teenagers has helped generate a market for "fake" drugs. These "look-alike" drugs are intentionally made to look like amphetamines, barbiturates, or other often-abused drugs. They are sold on the street and by mail order, and the seller often implies that they are the illegal drugs they resemble.

The look-alikes generally contain decongestants, caffeine, and other

stimulants in what FDA has called "dangerous, illogical combinations." Some contain alarmingly high doses of one ingredient. When taken in excess or mixed with alcohol, the look-alikes have caused strokes and death. They are extremely dangerous when mixed with, or replaced by, real "uppers" or "downers."

The availability and use of look-alikes make it harder for health professionals and law enforcement officials to combat the problem of illegal drug use. The AMA points out the following problems caused by look-alikes:

- School children and others who don't normally abuse drugs are told that the "look-alikes" are okay to use because they are legal and safe (in fact, they are neither).
- Look-alike drugs may make youngsters believe that the illegal drugs they mimic aren't as potent and dangerous as they really are.
- Traditional drug abuse education programs are hampered by the wide availability of the imitation drugs.
- Physicians and poison centers are deceived by the fake drugs, which makes drug-related diagnoses difficult.
- The look-alikes make it even more difficult for law enforcement officials to stop illegal drug traffic.

Most states have banned the manufacture and marketing of look-alikes, and the federal government has taken action against some manufacturers. But the availability of look-alike drugs is still a threat to the health and safety of teenagers.

RECOGNIZING QUACKERY

It is during the teenage years that people start to become serious consumers, and there's no better time to learn how to avoid quackery. Here are some tips:

- Be wary if immediate, effortless or guaranteed results are promised.
- Look for telltale words and phrases such as "breakthrough," "miracle," "secret remedy," "exclusive," and "clinical studies prove that . . ."
- Beware of promotions for a single product claimed to be effective for a wide variety of ailments.
- Don't forget that, unlike scientists and health professionals, quacks do not subject their products to the scrutiny of scientific research. The quack simply thrusts a product onto the market in order to get your money.
- Be cautious of money-back guarantees, for a guarantee is only as good as the company that backs it.
- If it sounds too good to be true—it probably is. ■

This article was prepared jointly by FDA and the Council of Better Business Bureaus.

For More Information

If you have questions about a product or company, get answers before you make a purchase. For information, contact:

- the Better Business Bureau
- the nearest Food and Drug Administration office
- your local consumer office or state attorney general's office
- your doctor.



The Notebook: a potpourri of items of interest gathered from FDA news releases, other news sources, and the Federal Register (designated FR, with date of publication). The Federal Register is available in many large public libraries.

■ FDA and the Centers for Disease Control have concluded that a plasma product called **RhoGAM** – used to prevent an uncommon condition of blood incompatibility in some pregnant women and their unborn children – did not cause a woman in the military and her child to be infected with the AIDS virus.

■ FDA has licensed the first **blood product** purified by using biotechnology – a blood-clotting factor that treats the hereditary clotting disorder hemophilia A.

■ The Beech-Nut Nutrition Corp. has been fined \$2 million – the largest fine ever under the Food, Drug, and Cosmetic Act of 1938 – after pleading guilty to charges that it sold **bogus apple juice**.

■ FDA's **Center for Drugs and Biologics** has been reorganized into two independent organizations – the Center for Drug Evaluation and Research, headed by Carl C. Peck, M.D., and the Center for Biologics Evaluation and Research, headed by Paul D. Parkman, M.D. Parkman is also coordinator of the agency's AIDS program.

■ Information on **patient package inserts** for prescription **estrogen drug products** will be made more readable and understandable under an FDA proposal. In addition, the new inserts will include updated information on the benefits and risks of estrogen drug use (FR Oct. 9).

■ FDA and the Bureau of Alcohol, Tobacco, and Firearms have reached an agreement that clarifies the responsibilities each agency has concerning **alcoholic beverages** (FR Nov. 30).

■ Special efforts by FDA to improve **dairy product safety** have helped reduce the number of dairy plants that produce contaminated finished products and improve the overall level of sanitation in the dairy industry, according to a report by FDA's Milk Safety Branch.

■ FDA no longer considers "requires prescription drug therapy" one of the criteria that would automatically require the marketer of a new drug to make a **serious adverse reaction report** to FDA. The agency feels this will eliminate many unnecessary reports without jeopardizing patient safety (FR Oct. 13).

■ FDA and the National Institute on Drug Abuse have proposed changes in the requirements and conditions for **methadone treatment**, including allowing detoxification treatment to continue for a maximum of 180 days instead of the current 21-day limit (FR Oct. 2).

■ Preparing for possible new regulations, the Occupational Safety and Health Administration is collecting information on ways to reduce the risk of **hepatitis B and AIDS** infection in health-care workers. In addition, OSHA and the Department of Health and Human Services are launching a nationwide educational campaign on existing regulations that health-care employers and workers should be following (FR Nov. 27).

■ The Consumer Product Safety Commission recently assumed responsibility for **"gut buster" exercise devices** that are supposed to strengthen stomach muscles and trim the waist. Because some injuries have occurred, CPSC is reviewing what safety measures can be used to regulate these devices.

■ FDA will not pursue the establishment of uniform **standards for electromedical devices** because the agency has not found sufficient evidence of health risks. In addition, the agency feels that manufacturers are adhering to existing voluntary standards (FR Oct. 15).

■ FDA has developed a suggested format for food additive, color additive, and generally recognized as safe (GRAS) affirmation petitions. **"Guidelines for the Preparation of Petition Submissions"** is available from the Center for Food Safety and Applied Nutrition (HFF-330), FDA, 200 C St., S.W., Washington, D.C. 20204 (FR Oct. 27).





Investigators' Reports

Homespun Sponges

by Catherine Carey

How could surgical sponges—supposedly free of any impurities—be contaminated with cat hairs, feathers and other, unidentified debris? They could, FDA discovered recently, if they were made not in a well-run manufacturing plant, but in the homes of the company's employees.

In November 1986, a medical center in Chattanooga, Tenn., complained to FDA that two packages of Qualtex Surgical Eye Spears (sponges) made by Ormed Manufacturing, Inc., of Buffalo, N.Y., contained hair, and two other lots had dark specks in them. When investigators with FDA's Nashville district office examined 119 packages elsewhere, they found 14 more packages with unidentified particles inside. Examination by FDA's Atlanta regional laboratory confirmed the presence of foreign material, including cat hair, feathers, unidentified blue fibers, and other debris.

At the same time, FDA also received reports from former Ormed employees that medical sponges were being manufactured not in the firm's plant, but in the employees' homes.

An investigator with FDA's Buffalo district office began examining sponges at Ormed on Feb. 19, 1987, but when he returned the next day he was not allowed to continue the inspection. Laboratory analysis of the sponges taken from the previous day confirmed filth in the form of cat hairs, human hairs, insects, and other particles. So the agency detained approximately \$250,000 worth of the sponges at the facility.

Ormed appealed the detention and requested a hearing. The company met with the Buffalo district staff on several occasions. After the last meeting, on March 2, 1987, Ormed sought a restraining order against FDA, requesting the detention be declared illegal. Hearings were held on March 3 before Judge John T. Curtin, Western District Court of New York at Buffalo. The judge directed both parties to come to an agreement by the next day.

FDA requested a seizure of the devices. The court agreed and ordered a U.S. mar-

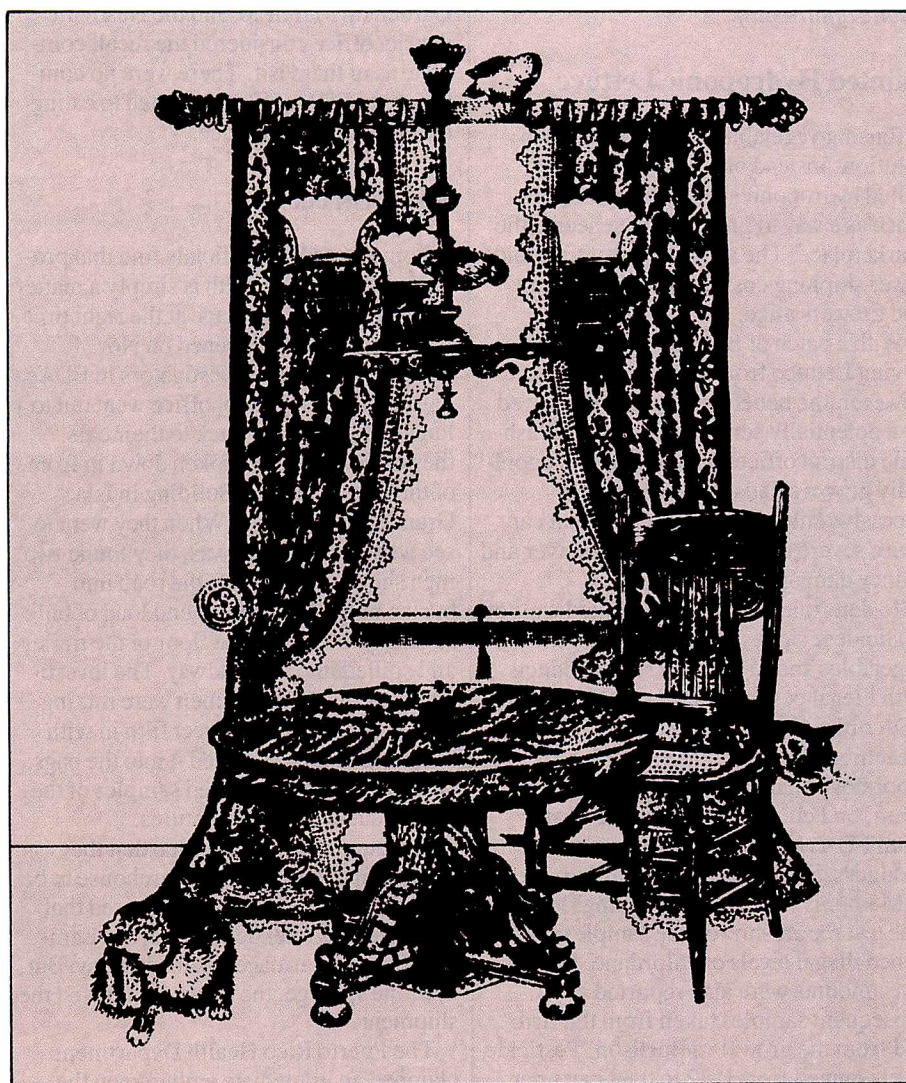
shal to seize all raw materials and all in-process and finished devices at Ormed's facility. These devices were valued at approximately \$1 million. The inspection had also confirmed that Ormed workers were indeed making the sponges in their homes and contaminating the products in the process. People hired to make the sponges would sit down at their kitchen or dining room tables to assemble them with instructions provided by the manufacturer. What were not provided were the sanitary controls used in a factory, such as hair nets and clean work tables.

As a result of FDA's investigation, the New York State Wage and Hour Board fined Ormed \$20,000 for labor law violations, the highest such fine ever imposed.

On March 24, after about three weeks of negotiations, separate consent decrees were signed by both Ormed and Med.

Tech, Inc., of Pennsylvania, a sales arm of Ormed. Both firms had filed claims to the seized merchandise. The inventory included, among other goods, eye spears, "peanut" sponges, and tonsil sponges used in eye, brain and throat surgery, respectively. The consent decrees stipulated that all materials made outside the manufacturer's facility must be relabeled "non-sterile" and sold for *non-medical* purposes only; finished products manufactured at Ormed must be examined and found to be free of contaminants before they could be released and raw materials could be released to the manufacturer only if they were also found to be free of contaminants.

Even though the sponges had been sterilized after Ormed received them from its employees, sterilization does not remove foreign particles, and FDA's concern was





the possible danger foreign particles in or on the sponges could pose if they remained in the body after surgery. Experts say such foreign particles left under closed incisions could produce allergic-type reactions and inflammation resulting in convulsions, breathing problems, scars, bowel obstructions, and tissue damage known as adhesions.

On March 25, the Buffalo district office told Ormed that the agency was prepared to seize more sponges found with contaminants. The firm decided to recall those lots instead, and subsequently recalled all sterile sponges made as far back as January 1986.

To date there have been no reported injuries to any patients. Ormed and Med. Tech., Inc., are currently operating under the terms of the consent decrees.

Catherine Carey is a member of FDA's public affairs staff.

Tainted Hydroponic Lettuce

Raising vegetables in greenhouses in solutions instead of soil — a technique called hydroponics — is gaining importance as a way to grow produce nearer the marketplace. The shorter transit time and lower shipping costs benefit consumers and growers alike.

With a batch of Boston Aqua Garden Living Lettuce from Burlison, Tenn., however, the benefits were overshadowed by a potentially serious risk. FDA's Nashville district office found those hydroponically grown salads-to-be contained excessive chlordane, a pesticide that can cause severe toxic effects, such as liver and kidney damage.

To determine the incidence and levels of pesticide residues in greenhouse-grown vegetables and to take any such products with illegal pesticide levels off the market, FDA ordered many of its offices in December 1986 to collect samples for laboratory analysis. As part of that program, on Feb. 24, 1987, an investigator from FDA's Memphis office visited the product's distributor, Aqua Garden, Inc., in Memphis to sample the "living" lettuce. The test report showed the sample contained illegal levels of chlordane. Excessive amounts were also reported in subsequent samples taken from the firm and from the grower in Burlison. Pesticide levels ranged from 0.32 to 0.39 parts per

million (ppm), which exceeds the FDA action level for chlordane in lettuce: 0.1 ppm.

Aqua Garden had distributed 93 cases of the contaminated lettuce to restaurants in the Memphis area and wholesalers in Alabama and Arkansas. The firm voluntarily stopped all sales and began recalling the product. The consignees were told to destroy all remaining stocks and any lettuce shipped to retail stores. Aqua Garden itself destroyed some 143 cases on hand by burying the lettuce in a local landfill.

The problem was attributed to airborne contamination from chlordane-treated soil outside the greenhouse in which the lettuce grew. The affected soil was removed.

The Tennessee Department of Agriculture assisted FDA with testing the various samples.

An FDA investigator checked the status of the recall in a follow-up visit to Aqua Garden on March 10, and the Nashville district office considered the recall complete as of that visit. There were no complaints to FDA of illness related to eating the contaminated lettuce.

Sweet Street

Sometimes FDA officials find that protecting the public health is simply a matter of being in the right place at the right time.

One such case happened on Nov. 4, 1986, when several investigators in FDA's San Juan, Puerto Rico, office went out to lunch. On their way back to their cars, they noticed a truck broken down in front of the Port Authority Building in Isla Grande, Puerto Rico. When they went to see what the problem was, they found two men shoveling sugar off the road into burlap bags. A 40,000-pound load of bulk sugar had collapsed the floor of the trailer and spilled into the roadway. The investigators noticed that the men were mixing dirt, rocks, and other street filth in with the sugar as they shoveled it into the bags. One investigator collected samples of the spilled sugar and took pictures.

He found out from the men that they were taking the sugar to a warehouse to be stored. Further tracking discovered that the sugar was intended for Warner Lambert Inc., a pharmaceutical company. But, after the spillage, the company refused the shipment.

The Puerto Rico Health Department clamped an immediate embargo on the

sugar until FDA could get a court order to have it seized.

In its petition to the U.S. District Court for the District of Puerto Rico, FDA charged that the sugar was adulterated and had been held under insanitary conditions.

No laboratory analysis was necessary; the photos and sample of the sugar were all the evidence the court needed. The seizure was ordered May 15, 1987.

No one has claimed the sugar, and it is now awaiting destruction.

Mice Say Cheese for FDA

The photographs FDA investigators took at the Ciales Cash and Carry food warehouse in Ciales, Puerto Rico, were not the sort to be placed fondly on the mantelpiece. The graphic depiction of grossly unsanitary conditions helped FDA take legal action against the firm and unsettled the stomach of the judge handling the case.

In early March 1987, two investigators from FDA's Puerto Rico office inspected the warehouse, which supplies two chain supermarkets and other retail stores in Ciales and neighboring cities. They found signs of massive rodent infestation in the area that held products such as rice, sugar, beans, and hog feed: mice coming and going at will; dead rats and mice in various stages of decomposition; a rodent nest with newborn pups; and products in bags that were urine-stained, gnawed on, and covered with rodent excrement.

When the investigators provided the firm's owner with a list of the objectionable conditions, he agreed to correct the problems, and the firm destroyed three lots of contaminated food while the investigators watched. Another 11 lots of human food and animal feed were embargoed by the Puerto Rico Health Department after analysis of samples collected by the investigators confirmed that the food contained rodent filth.

In early May, an investigator returned to the warehouse to see if conditions had improved. The owner claimed he had a contract with a new exterminating service and that all possible rodent entryways had been sealed. But when the investigator looked for himself, the rodent population seemed as well-entrenched and happy as ever. There were numerous places they could enter and exit, evidence of rodent teeth at work on bags of rice and potatoes,



and rodent nesting material.

Further, when the investigator asked about the products placed under embargo in March, he was told that they had either been returned to suppliers for credit, sold, or otherwise disposed of, with no authorization from the health department.

At FDA's request, a U.S. marshal seized all food valued at about \$125,000 in the warehouse. The firm signed a consent decree agreeing not to resume business until it had cleaned its premises and provided proper sanitary controls. However, scarcely a month later, FDA received a report that the warehouse was doing business as usual and sent an investigator out to check. When the investigator found the firm was receiving new lots of food, mixing them with the seized lots, and selling them, FDA brought legal charges against the firm.

In a hearing on July 24, San Juan investigators testified as to the unsanitary conditions at the warehouse and produced dozens of photographs to make their point. The judge, who complained that the photographs had ruined his appetite for lunch, requested that the case be settled immediately. The conditions stipulated by the government to which Ciales agreed were to pay \$10,000 for violating the seizure order and reimburse the government \$1,500 for expenses the firm had caused. The judge also ordered the firm to obtain a \$250,000 bond within three days or be fined an additional \$10,000 a day. The firm obtained the bond and agreed not to resume business until it had cleaned its premises.

Mouse Rockefeller

Spinach is often combined with many other ingredients — oysters, cream sauce, bacon bits, cheddar cheese — to make delectable dining delights. But an unpleasant ingredient one company's employees found mixed with the firm's chopped spinach turned, rather than

delighted, their stomachs.

The unpleasant culinary discovery was made in October 1986 by employees at The All American Gourmet Company, in Clearfield, Utah, as bulk spinach was being creamed and added to the firm's Yankee Pot Roast Dinners. Mixed in with the spinach were rodent chunks measuring $1\frac{1}{4}$ inches by $\frac{3}{4}$ inch and $1\frac{1}{4}$ inches by $\frac{1}{2}$ inch. The firm notified the U.S. Department of Agriculture (USDA), which has jurisdiction over meat and poultry products. USDA detained the finished dinners and asked FDA to deal with the bulk spinach.

Investigators from FDA's Salt Lake City office collected samples of the bulk spinach, which the firm was voluntarily holding from the market. In addition to the rodent pieces, closer inspection also found rodent hair.

The spinach had been processed — washed, inspected, blanched, chopped and packaged — by Seabrook Brothers & Sons, in Seabrook, N.J. FDA's Camden, N.J., office had inspected the firm earlier that year and found no problems. However, when investigators returned in November, they found that the firm's methods for inspecting the spinach were inadequate and that it was quite possible

the mice had been "harvested" with the bulk spinach from the field and had accidentally been "processed" along with the vegetable. (The firm has since improved its inspection methods.)

At FDA's request, two lots of spinach were seized Dec. 19. They were claimed by Seabrook Brothers, who questioned FDA's findings and asked permission to take samples for further analysis. Before the firm had the opportunity to do this, however, an employee with All American Gourmet again found bits of mouse mixed in with spinach, this time intended to be part of frozen chicken au gratin dinners. The firm again contacted USDA, which detained about 3,000 cases of the dinners. (These were eventually destroyed.) The company destroyed the bulk spinach the next day, under supervision of a USDA inspector.

On June 7, All American Gourmet destroyed 42,662 cases of the frozen pot roast dinners detained by USDA. Twenty days later, at FDA's request, the bulk spinach seized in December was buried in the Clearfield-Layton dump in Utah.

— This small sample of reports from the field was compiled by Carol Ballentine, Catherine Carey, Dixie Farley, and Shelly Maifarh.





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.

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: Copra meal for animals, at Campbell Industrial Park, Hawaii, Dist. Hawaii; Civil No. 86-0756.

CHARGED 10-22-86: While held for sale, the article contained the added poisonous or deleterious substance polychlorinated biphenyls—402(a)(2)(A).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65044; S. No. 86-497-148; S.J. No. 1)

PRODUCT: Corn, shelled, at Boston, M. Dist. Ga.; Civil No. 85-78-THOM.

CHARGED 11-8-85: When returned from Live Oak, Fla., to South Georgia Peanut Co., Boston, Ga., the article contained the added poisonous and deleterious substance aflatoxin, which might render it injurious to health—402(a)(1).

DISPOSITION: Consent—authorized release to the possessor for bringing into compliance. (F.D.C. No. 64789; S. Nos. 86-333-877/9; S.J. No. 2)

PRODUCT: Swordfish slabs, frozen (two lots), at Ellsworth, Dist. Maine; Civil No. 87-0030-B.

CHARGED 1-30-87 and amended 1-10-87: When shipped by Texas

Shellfish, Houston, Texas, and Calypso Seafood International, Inc., Boston, Mass., both lots of the article contained the added poisonous and deleterious substance methyl mercury, which might render the article injurious to health—402(a)(1).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65109; S. No. 87-518-452; S.J. No. 3)

Foods/Contamination, Spoilage, Insanitary Handling

PRODUCT: Apple slices, dried, Del Monte, at Topeka, Dist. Kan.; Civil No. 86-4214.

CHARGED 7-8-86: When shipped by Del Monte, San Jose, Calif., the article was unfit for food due to an obnoxious odor (excessive sulfites)—402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 64922; S. Nos. 86-491-073/4; S.J. No. 4)

PRODUCT: Crab meat, special, claw, backfin, lump, or cocktail claw fingers, at Irvington, S. Dist. Ala.; Civil No. 86-0856-14.

CHARGED 9-25-86: While held by Southern Aire Seafood, Irvington, Ala., the articles had been prepared and packed under insanitary conditions—402(a)(4).

DISPOSITION: The articles were claimed by the dealer and Jerry Lyons, who denied the charge and objected to the search for and the seizure of the articles. Pursuant to a motion by the claimants, post-seizure sampling of the articles was ordered. The claimants moved for an order directing that the government give prior notice of any subsequent seizure of crab meat at Southern Aire. The court denied the claimants' motion, citing *Southeastern Minerals, Inc. v. Harris*, 622 F.2d 758, 763 (5th Cir. 1980), and basing the denial upon the record and the government's response.

The government served requests for admissions on the claimant. Following a pretrial conference, the claimants were granted 10 days in which to address the evidentiary problems raised by the government and in which to seek leave to file a counterclaim; the government was granted a like period of time to respond. The claimants filed a motion for leave to file a counterclaim in the amount of \$8,718, alleging that after the approximately 1,453 pounds of crab meat had been seized, it had been transported in a truck that was not air-conditioned on a 92-degree-Fahrenheit day from Irvington, Ala., to frozen storage at Mobile, Ala.

The court denied the claimants' counterclaim motion because such a permissive counterclaim appeared to be premature under the circumstances and would unnecessarily and inappropriately complicate the litigation. The court also considered the eviden-



tiary issue of whether the testimony of certain of the claimants' regular customers (who had received crab meat in the week before the seizure) was relevant. The court concluded that such testimony was irrelevant and was, therefore, inadmissible. Subsequently, a consent decree of condemnation ordered the articles destroyed. (F.D.C. No. 65029; S. No. 86-376-104 et al.; S.J. No. 5)

PRODUCT: Peanuts, shelled and unshelled, at Suffolk, E. Dist. Va.; Civil No. 86-743-N.

CHARGED 10-16-86: While held by Nansemond Cold Storage, Inc., Suffolk, Va., all of the articles had been held under insanitary conditions, and some lots of the articles contained rodent or insect filth—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65049; S. No. 86-339-174 et al.; S.J. No. 6)

PRODUCT: Peanuts, sunflower seeds, and other food stocks, at Suffolk, E. Dist. Va.; Civil No. 87-103-N.

CHARGED 2-19-87: While held by Virginia Peanut Processors, Inc., Suffolk, Va., the articles had been held under insanitary conditions, and a number of the articles contained insect or rodent filth—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65121; S. No. 87-516-002 et al.; S.J. No. 7)

PRODUCT: Pinto beans, Great Northern beans, and field peas, at LaFayette, W. Dist. La.; Civil No. 87-1140.

CHARGED 6-2-87: While held by B.F. Trappey's Sons, Inc., LaFayette, La., the articles had been held under insanitary conditions—402(a)(4); and the field peas contained rodent filth—402(a)(3).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65194; S. No. 87-519-070 et al.; S.J. No. 8)

PRODUCT: Rye bread, Italian rolls, sandwiches, and other prepared foods, in-process foods, and food components, at Philadelphia, E. Dist. Pa.; Civil No. 87-2925.

CHARGED 5-15-87: While held by Hotstuf Foods, Inc., Philadelphia, Pa., the articles had been prepared, packed or held under insanitary conditions—402(a)(4); and the labels of one lot of sandwiches lacked the name and place of business of the manufacturer, packer or distributor, and lacked the common or usual name of each ingredient—403(e)(1), 403(i)(2).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65201; S. No. 81-450-682 et al.; S.J. No. 9)

PRODUCT: Spinach, chopped, frozen, in bulk, at Clearfield, Dist. Utah; Civil No. 86-NC-160S.

CHARGED 12-19-86: When shipped by Seabrook Brothers & Sons, Inc., Seabrook, N.J., the article contained rodent filth—402(a)(3).

DISPOSITION: The article was claimed by the shipper, who denied the charge and petitioned for post-seizure samples. Ultimately, a consent decree of condemnation ordered the articles destroyed. (F.D.C. No. 65092; S. Nos. 87-472-727/8; S.J. No. 10)

PRODUCT: Tomatoes, peeled, canned, at Jacksonville, M. Dist. Fla.; Civil No. 86-721-Civ-J-16.

CHARGED 6-25-86: When shipped from Charleston, S.C., the article, labeled "Eastwinds Brand Peeled Plum Tomatoes Choice Product of Spain . . . Distributed By Connell Rice & Sugar Co., Inc., Westfield, N.J.," was unfit for food due to swollen cans—402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 64927; S. No. 86-436-538; S.J. No. 11)

Foods/Economic and Labeling Violations

PRODUCT: Concentrated "orange juice" for manufacturing, at Ventura, C. Dist. Calif.; Civil No. 83-0403FW.

CHARGED 1-21-83: When shipped by Citro Florida, Inc., San Antonio, Texas, the article (labeled "COJM Grade A . . . Citro Florida, Inc. Frostproof, Florida") had color (turmeric) added to the article to make it appear better or of greater value than it was—402(b)(4); the article contained the nonconforming color additive turmeric since no regulation permitting the addition of turmeric to concentrated orange juice for manufacturing (COJM) was in effect—402(c); the article's labeling was false and misleading, since the product name "COJM" represented and suggested that the article was concentrated orange juice for manufacturing, but it contained the artificial color turmeric—403(a)(1); the article failed to conform to the definition and standard of identity for COJM, since it contained the added color turmeric—403(g)(1); and the article contained the artificial color turmeric and its label failed to state that fact—403(k).

DISPOSITION: The article was claimed by Ventura Coastal Corp., Ventura, Calif., who admitted that the article contained turmeric, denied that the article was adulterated, and admitted that the manufacturer's labeling failed to include the artificial color designation (although denying that the article was something other than concentrated orange juice for manufacturing, denying that it failed to conform to its standard of identity, and denying that it was misbranded). The claimant served requests for admissions and written interrogatories on the government. Subsequently, a consent decree of condemnation authorized the release of the article to the claimant for bringing into compliance. (F.D.C. No. 63613; S. No. 81-258-347 et al.; S.J. No. 12)

PRODUCT: Trout, fillets, "smoked," canned, at Hamilton, Dist. Mont.; Civil No. 87-61-M-CCL.

CHARGED 3-27-87: While held by Hayes Ranches, Inc., Hamilton, Mont., who had processed the article using interstate trout fillets, the article's labeling was false and misleading in representing that the article was smoked, since it had not been smoked, but had been soaked in artificial smoke flavor (pyroligneous acid)—403(a)(1); and the article's label lacked the common or usual name of the food and the common or usual name of each ingredient, because the article was artificially smoke-flavored trout (not smoked trout) and the ingredient artificial smoke flavor had not been listed on the label—403(i)(1) and (2).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65130;



S. No. 87-370-543; S.J. No. 13)

Drugs/Human Use

PRODUCT: Ephedrine HCl tablets, at Jackson, S. Dist. Miss.; Civil No. J86-0783(B).

CHARGED 11-20-86: While held for sale, the article was an imitation of methamphetamine and amphetamine—502(i)(2).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65071; S. No. 87-355-510; S.J. No. 14)

PRODUCT: Ethynodiol diacetate & mestranol combination tablets, two seizure actions, at Glasgow, W. Dist. Ky., and Elk Grove Village, N. Dist. Ill.; Civil Nos. C84-0236 BG(S) and 85-C-1890.

CHARGED 11-19-84 and 3-5-85: The article was a counterfeit drug, and the article, its contents, and its labeling, without authorization, bore the trademark, trade name, imprint or likeness of a drug manufacturer other than the actual manufacturer, packer, labeler or distributor—201(g)(2).

DISTRIBUTION: Defaults—ordered destroyed. (F.D.C. Nos. 64426 and 64522; S. Nos. 85-326-556 and 85-362-630; S.J. No. 15)

PRODUCT: Hydrocortisone and pramoxine HCl topical ointment, at Gravette, Ark.; Civil No. 87-5060.

CHARGED 5-6-87: When shipped by Topiderm, Inc., Bohemia, N.Y., the article, which was being labeled by Dunhall Pharmaceuticals, Inc., Gravette, Ark., as "1+1 Hydrocortisone Pramoxine Hydrochloride Creme . . . Manufactured for: Dunhall Pharmaceuticals, Inc. . . . by Topiderm, Inc., Bohemia, New York," was a new drug without an effective approved New Drug Application—505(a).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65178; S. No. 87-519-278; S.J. No. 16)

PRODUCT: Lubraseptic antibacterial lubricant, at Van Nuys, C. Dist. Calif.; Civil No. 87-00642-JGD(Gx).

CHARGED 1-30-87: While held by Lamar Labs., Van Nuys, Calif., the article, which was accompanied by labeling such as (leaflet) "Lamar Labs . . . Here's news of importance," (brochure) "Lubraseptic's Antibacterial Formula Shown in Laboratory Tests to Kill AIDS Virus," and (brochure) "In-Vitro Test Results," was a new drug without an effective approved New Drug Application—505(a); and the article's labeling lacked adequate directions for its intended use, and the article was not exempt due to its new drug status—502(f)(1).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65111; S. No. 87-425-976; S.J. No. 17)

PRODUCT: Starch blocker tablets, at Provo, Dist. Utah; Civil No. C82-0889A.

CHARGED 9-21-82: When shipped by R-Kane Products, Inc., Pennsauken, N.J., the article, labeled "Super Strength Starch Blocker Amylite™ . . . Distributed By Teltex, Inc., Provo, Utah," was a new drug without an effective approved New Drug Application—505(a).

DISPOSITION: The article was claimed by Teltex, Inc., Provo, Utah, who denied the charge. Following the settlement of a suit between the shipper of the article and its claimant, Teltex, Inc., transferred its interest in the article to the shipper. Ultimately, the court of appeals in a related case affirmed that starch blocker tablets were new drugs, and the article was destroyed. (F.D.C. No. 63810; S. No. 82-243-669; S.J. No. 18)

PRODUCT: Starch blocker tablets, two seizure actions, at Carbondale, S. Dist. Ill., and Redford, E. Dist. Mich.; Civil Nos. 82-4280 and 82-73661.

CHARGED 9-24-82 and 9-29-82: When shipped by Sunrise Chemical, Deer Park, N.Y., or other interstate shipper, the articles (some of which were labeled "AMX Tablets . . . Sunrise Chemical . . . Deer Park, NY," or "Nutrition Headquarters Starch Blocker Tablets," or "Starch-Ex Protein Concentrate Nutritional Limits Starch Conversion . . . Packed by Timepak Company, Detroit, MI . . . Distributed By O'Connor Pharmaceuticals, Redford, MI") were new drugs without effective approved New Drug Applications—505(a).

DISPOSITION: A default decree in the Redford action ordered the seized articles destroyed. In the Carbondale action, Nutrition Headquarters, Inc., Carbondale, Ill., filed a claim and requested transfer of the action to the Southern District of New York for consolidation with a suit for declaratory judgment. The action was transferred to the Southern District of New York. Following the affirmance upon appeal of a favorable judgment for the government, the articles in the Carbondale action were destroyed. (F.D.C. No. 63793; S. Nos. 82-249-222, 82-294-164; S.J. No. 19)

Drugs/Veterinary

PRODUCT: Parenteral veterinary drugs, at LeSueur, Dist. Minn.; Civil No. 4-84-260.

CHARGED 3-16-84: When shipped by International Multifoods, Omaha, Neb., the articles (labeled "Hypertonic Dextrose . . . Sterile . . . Osborn . . . International Multifoods Minneapolis, Mn.," "Kalamino Calcium With Electrolytes . . . Sterile . . . Osborn . . . International Multifoods Minneapolis, Mn.," "Bal-Amino 1000 Injectable Concentrate . . . Sterile . . . AGRiPharm . . . International Multifoods Minneapolis, Mn.," and "Kal-Dex-Calcium Buffered With Electrolytes . . . Osborn . . . International Multifoods Minneapolis, Mn.") had been manufactured, processed, packed and held under circumstances that failed to conform with current good manufacturing practice—501(a)(2)(B). **DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 64214; S. No. 84-304-355 et al.; S.J. No. 20)

PRODUCT: Premix veterinary drugs, at Storden, Dist. Minn.; Civil No. 4-84-560.

CHARGED 6-11-84: While held by Storden Farm Center, Inc., Storden, Minn., the circumstances used for the manufacture of the articles failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: The articles were claimed by the dealer, who admitted the allegation of the government's complaint (except that all of the articles were alleged by the claimant to be salvageable).



Subsequently, a consent decree authorized release of the articles for salvaging. (F.D.C. No. 64245; S. No. 84-360-449 et al.; S.J. No. 21)

Medical Devices

PRODUCT: Endotracheal tubes with cuffs, at Chicago, N. Dist. Ill.; Civil No. 84-C-3278.

CHARGED 4-18-84: The articles had been manufactured and subsequently recalled by Lifeline Products, Inc., Prospect Heights, Ill., and the quality of the articles fell below their purported quality, since the articles were labeled as "cuffed" and "sterile," but their cuffs leaked and their packaging contained holes and open seals—501(c); and the articles were dangerous to health when used as directed in the labeling—502(j).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 64226; S. No. 84-384-144 et al.; S.J. No. 22)

PRODUCT: Intraocular lenses, at Huntington Beach, C. Dist. Calif.; Civil No. 85-5093 DWW(Gx).

CHARGED 8-2-85: The articles (which had been manufactured in Mexico and which were being held by Americal IOL International, Huntington Beach, Calif.) had been manufactured for, and marketed by, the dealer as investigational devices, pursuant to investigational device exemptions; but the dealer failed to comply with prescribed regulations (e.g., specified monitoring procedures, quality control procedures, and follow-up procedures as to complaints/adverse reactions)—501(i).

DISPOSITION: The article was claimed by Bionica International, S.A. (a subsidiary of the dealer), Mexicali, Mexico, who denied the charge and asserted that the devices were covered by an exemption and customs bond at the time of arrival in the United States. Subsequently, a consent decree of condemnation authorized release of the article to the claimant for salvaging. Ultimately, all of the articles (except for a number of historical samples) were destroyed. (F.D.C. No. 64682; S. No. 85-303-517; S.J. No. 23)

PRODUCT: Thermometers, oral, at Plattsburgh, N. Dist. N.Y.; Civil No. 86-CV997.

CHARGED 9-5-86: The article had been shipped by Tsubasa Industry Co., Ltd., Tokyo, Japan; and the quality of the article, labeled (carton) "Unipack Corp. New York . . . Made in Japan" and (device) "LC Oral 1/2 Min Japan," failed to meet established accuracy requirements for such devices—501(c).

DISPOSITION: Consent—authorized release to Unique Packaging Corp., Plattsburgh, N.Y., for export to the original foreign supplier. (F.D.C. No. 64898; S. No. 86-469-907; S.J. No. 24)

CRIMINAL ACTIONS

PRODUCT: Bueno Foods Old Mexico Brand, Inc., and Lee Urias Jr., president and manager, El Paso, W. Dist. Texas; Criminal No. EP-86-CR-08.

CHARGED 1-16-86: While held for sale, bales of corn husks for tamales (counts 1 and 2), dried chile arbol (count 3), dried chile peppers (count 4), tostada chips (count 5), piloncillo candy (count 6), and boxes of corn husks (count 7) were held under insanitary

conditions in a building accessible to insects and/or rodents and exposed to contamination by insects or rodents; and the bales of corn husks in count 2 were contaminated with rodent filth—402(a)(3), 402(a)(4).

DISPOSITION: The defendants pleaded not guilty. The case came on for trial by the court. The court found the defendants **not guilty** as to count 1 and guilty as to counts 2 through 7. The corporation was fined \$6,000. The individual was sentenced to one year in prison (suspended), was fined \$6,000, and was placed on probation for five years with 300 hours of community service as a special condition. (F.D.C. No. 64555; S. No. 83-296-880 et al.; S.J. No. 24)

INJUNCTION ACTIONS

DEFENDANTS: Medical Systems Research, Inc., and Legrand K. Holbrook, president, North Salt Lake City, Dist. Utah; Civil No. C-85-0336A.

CHARGED 3-22-85 in a complaint for injunction: That the defendants manufactured, processed, packed, labeled, stored, held for sale, and distributed in interstate commerce Steri-Stat (Health Care Personnel Handwash with 0.8% w/v chlorhexidine gluconate); that Steri-Stat was a new drug without an effective approved New Drug Application; that Steri-Stat's labeling lacked adequate directions for use and the article was not exempt due to its new drug status; and that the defendants were well aware of the violative new drug status of Steri-Stat, but had continued their distribution of Steri-Stat—505(a), 502(f)(1).

DISPOSITION: Pursuant to stipulation of the parties, the defendants were to refrain for three years from shipping any drug until at least 20 days after providing specified descriptive material to the FDA district, and were to refrain from distributing Steri-Stat or any other chlorhexidine gluconate drug unless and until the defendants had complied with specified new drug regulations and all such drugs on hand had been brought into compliance with the law. (Inj. No. 1097; S. No. 84-392-059 et al.; S.J. No. 25)

DEFENDANTS: U.S. Macaroni Manufacturing Co., and Joseph A. DeFelice, president, **Albert O. DeFelice**, vice president, and **Arthur G. DeFelice**, secretary-treasurer, Spokane, E. Dist. Wash.; Civil No. C-86-760-RJM.

CHARGED 9-15-86 in a complaint for injunction: That the defendants (after interstate shipment of component flours) prepared, packed, held for sale, and distributed in interstate commerce finished pasta products (e.g., macaroni, spaghetti and noodles); that FDA inspections revealed continued insect infestations at the defendants' facility; and that the history and current conditions at the facility indicated that, unless enjoined, the violations would continue—402(a)(4).

DISPOSITION: A consent decree of permanent injunction enjoined the violations complained of and enjoined operations involving interstate foods unless and until a number of specified conditions were met, including: the facility was cleaned and renovated, an expert certified that an adequate sanitation control program had been implemented, and all contaminated food on hand was destroyed or otherwise brought into compliance. (Inj. No. 1146; S. No. 86-464-523 et al.; S.J. No. 26)

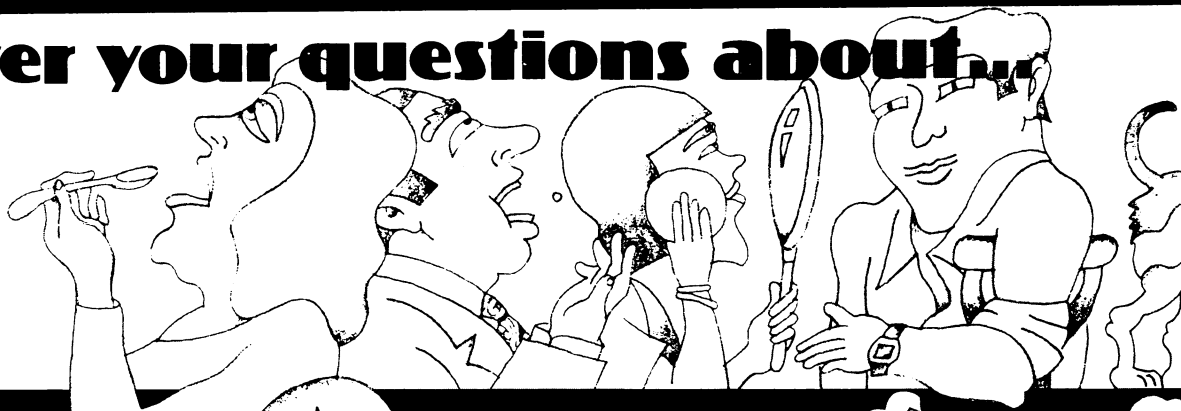
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advisers
trouble spotters
complaint checkers—
and other good authorities



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food, drugs, biologics, medical
devices, cosmetics, products
that emit radiation, veterinary
drugs, and animal feed
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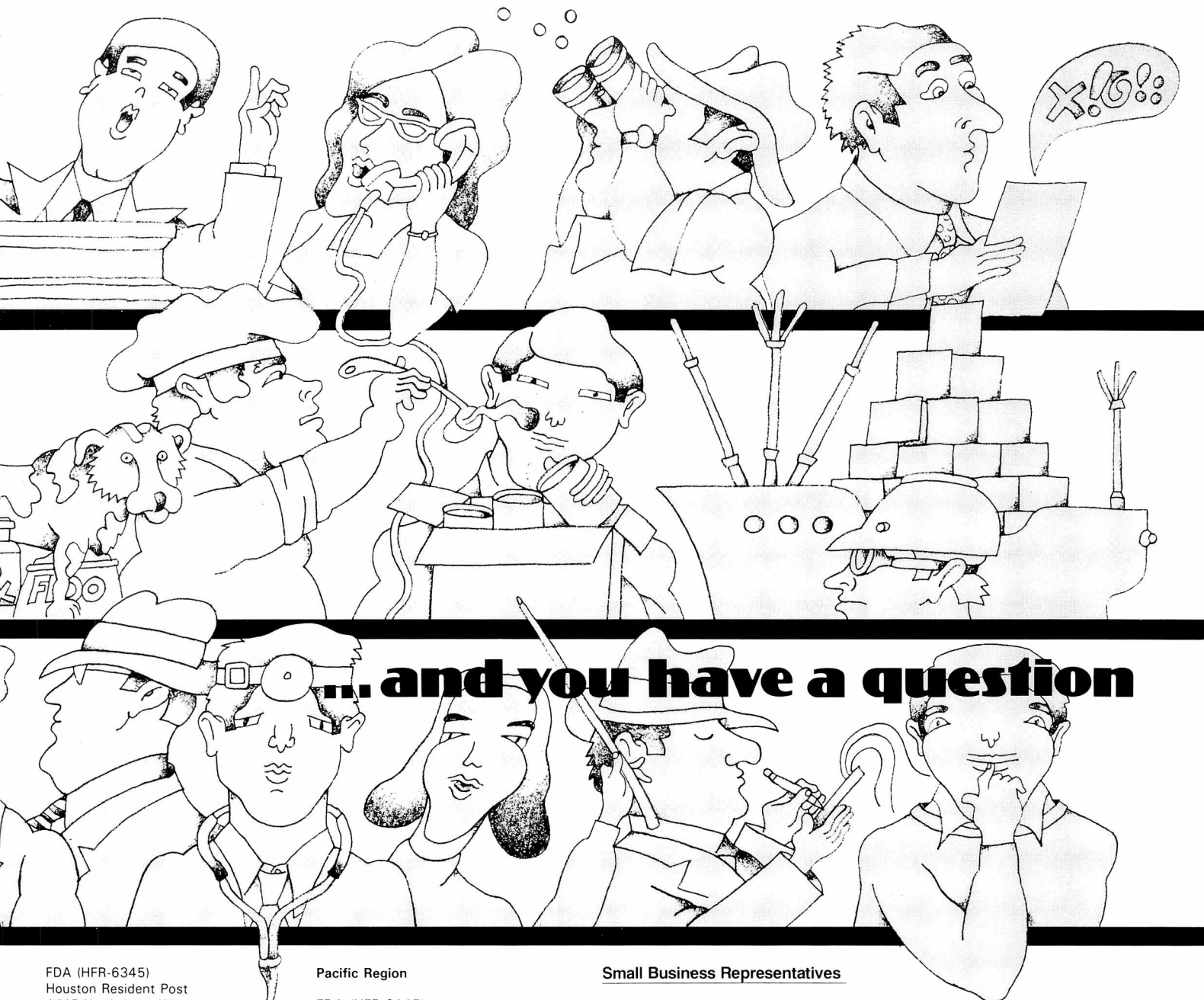
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