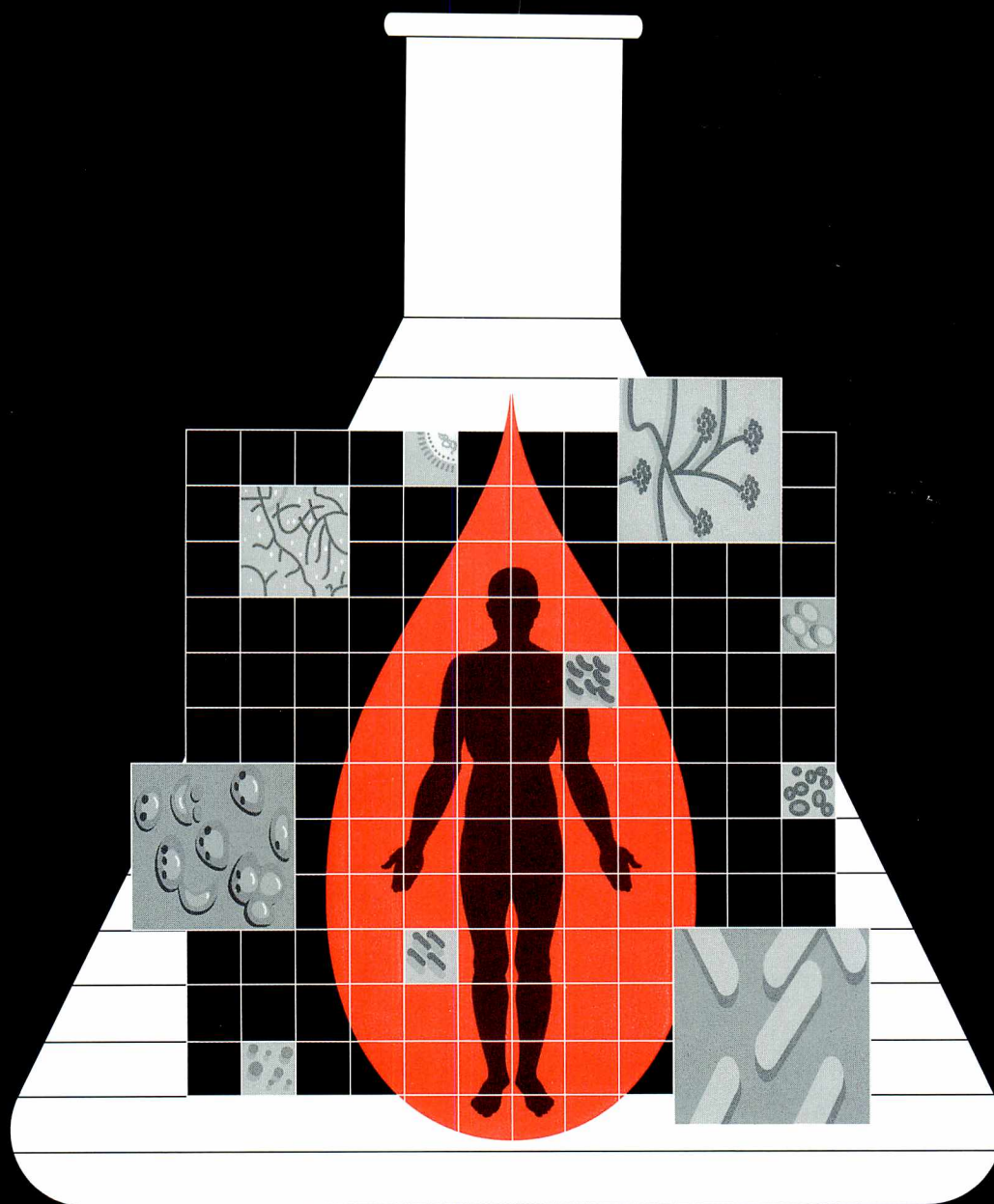


FDA CONSUMER

• VOL. 23 NO. 6

JULY-AUGUST 1989 •



TOP 10 LABORATORY TESTS

Blood Will Tell



Louis W. Sullivan, M.D.
Secretary of Health and
Human Services

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

Jeff Nesbit
Associate Commissioner for
Public Affairs

Marian G. Segal/Acting Editor

Jesse R. Nichols/Art Director

Michael L. Herndon/Production Manager

Carol L. Ballentine/Copy Editor

Cover Design: Zebulon Rogerson

FDA Consumer (ISSN 00362-1332) is published by the Food and Drug Administration, U.S. Public Health Service, Department of Health and Human Services. It is published monthly, except for combined issues for July-August and December-January. Use of funds for printing *FDA Consumer* has been approved by the Office of Management and Budget.

Editorial Matters

Address for editorial matters is *FDA Consumer*, Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, Md. 20857. Articles in *FDA Consumer* may be republished without permission. Credit to *FDA Consumer* as the source is appreciated. *FDA Consumer* is indexed in the *Reader's Guide to Periodical Literature*.

Subscriptions

Send inquiries concerning subscription problems or address changes to Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Include mailing label from the back cover for address changes.

To keep subscription prices down, the Government Printing Office mails each subscriber only one renewal notice. To determine when you will get your renewal notice, check the number that follows ISSDUE on the top line of your mailing label. When the label reads ISSDUE003, a renewal notice will be sent. When the label reads ISSDUE000, you have received your last issue unless you renew.

To continue to receive *FDA Consumer* without interruption, please return your renewal notice promptly. If your subscription has expired, simply send your mailing label with \$12 (\$15 foreign), using the form on the back cover, to Superintendent of Documents, Government Printing Office, Washington, D.C. 20402, and your service will be reinstated.

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

VOL. 23 NO. 6

JULY-AUGUST 1989

In Day-Care Centers, Cleanliness Is a Must 5

Dirty diapers in day-care centers can be more than just a nuisance if center staff don't follow commonsense rules for good hygiene and sanitation. As Commissioner Young explains, carelessness can lead not just to diarrhea in the center, but to serious health problems in the whole community.

The Cyanide Scare: A Tale of Two Grapes 7

A threatening phone call in Santiago, Chile, set in motion the biggest food safety investigation in FDA's history. In less than three weeks' time, nearly 8 million cases of Chilean fruit were examined for cyanide tampering. No one was injured, and, in the end, the system worked.

Mumps Makes a Comeback 12

With the institution of mumps vaccination programs in the late 1970s, cases of the disease declined steadily for several years. But this so-called "childhood disease" is coming back, only to a different age group—primarily young adults.

The Puzzling Picture of Multiple Sclerosis 17

When nerves in the brain and spinal column lose their protective coating, the effects may show up as numbness, double vision, paralysis, or pain. The condition is called multiple sclerosis, and scientists are piecing together new clues about what causes this debilitating, still incurable disease.

Top 10 Laboratory Tests: Blood Will Tell 22

What does that blood sample say about the state of your health? To a trained expert—or a sophisticated machine—it may signal anything from a minor infection to a heart attack, or a myriad of problems in between. No wonder blood "chemistries" top the list of the most frequently performed lab tests.

What Can Be Done When the Pain Won't Go Away? 28

Pain isn't always bad—it can alert us that something is wrong with our bodies. From the sharp stab of a cut finger to the dull ache of weary muscles, pain sends a message. But when persistent pain serves only to torment us, we need help. Here's a look at what's available and what's on the horizon.

Updates	2	Investigators' Reports	33
AIDS Page	4	Summaries of Court Actions	37
Notebook	32		

← Inside Front Cover Photo:

Something besides orders for wheat was being passed around the Chicago Mercantile Exchange in October 1987. Some traders were exchanging the mumps virus as well. For more about this and other mumps outbreaks among young adults, see page 12. (Photo by Steve Leonard, Black Star)



Change Urged in Use of Two Drugs

FDA has urged physicians to limit the use of two heart disease drugs to patients with life-threatening arrhythmias (abnormal heartbeat). The drugs — flecainide (sold as Tambocor by Riker Laboratories, Inc.) and encainide (sold as Enkaid by Bristol-Myers Co.) — should not be used in patients with less severe problems, even though they may have symptomatic heart disease.

FDA's recommendation was based on findings of a study which showed that patients with non-life-threatening arrhythmias who received either of the drugs were more than twice as likely to die of a heart attack as were patients who received a placebo. The study findings confirmed, however, that the drugs are safe and effective for treating severe arrhythmias, such as ventricular tachycardia.

The study was overseen by the National Heart, Lung, and Blood Institute. It was designed to determine if suppressing or eliminating abnormal heartbeats in patients who had recently had a heart attack would improve their survival. The results showed, however, that 56 of 730 patients given encainide or flecainide for an average of 10 months had died, compared to only 22 deaths among 725 patients who received a placebo.

The two drug manufacturers are sending letters, developed in consultation with FDA, to physicians advising them of the recommended changes in use of the drugs. In addition, the companies are modifying the drugs' labeling.

FDA cautions that patients taking either of these medications should not change dosage or discontinue use without consulting their physicians. The drug makers estimate that some 200,000 people are receiving one or the other of the drugs.

Hydrogen Peroxide Warning

FDA is warning consumers about a product being illegally promoted for treating AIDS, cancer, and other conditions. The product, which contains industrial-grade hydrogen peroxide — a corrosive material more than 10 times stronger than the commonly used antiseptic solution — has caused at least one death and several injuries among children in Texas.

The agency learned of the injuries and death while trying to stop distribution of the product by a Brownsville, Texas, firm. Two brothers in Dennison, Texas, were hospitalized for six months after drinking the solution.

Their sister, aged 4, had poured it for them from a quart bottle in the refrigerator, mistaking it for ice water. A woman in Conroe, Texas, made the same mistake when she served the hydrogen peroxide to her children and a neighbor's child. Her children were severely injured, and the neighbor's child died.

Distributors of the product claim that drinking the solution daily in diluted form can treat not only AIDS and cancer, but also acne, gum disease, athlete's foot, colic, headache, and varicose veins. No information supporting these claims has been submitted to FDA. (For more on AIDS quackery, see "Defrauding the Desperate: Quackery and AIDS" in the October 1987 *FDA Consumer*.)

Shelf-Life Dating of Condoms

U.S. condom manufacturers intend to add shelf-life dating to the labels of their products as soon as practicable. The voluntary action, announced by the Health Industry Manufacturers Association (HIMA), a trade group to which all domestic condom manufacturers belong, will tell consumers the date beyond which reliability of the product is uncertain. Condom shelf life is believed to range between three and five years or longer.

In a letter to FDA's Center for Devices and Radiological Health, HIMA said condom makers have begun analyzing stability data on a wide range of latex formulations and potential lubricants to develop testing methods that will accurately predict shelf life.

New Drug Division

In an effort to streamline the approval of new drugs, the Center for Drug Evaluation and Research last April established a new division for drug evaluation.

The new division, known as the pilot review division, will review anti-inflammatories, analgesics, anesthetics, and drugs with abuse potential (such as codeine, morphine and Valium). The division will be a testing ground for various ideas for streamlining and improving the drug evaluation process. John Harter, M.D., will serve as acting head of this new pilot division.

The impetus for streamlining the drug approval process for life-threatening diseases such as AIDS and cancer stems in part from recent recommendations of the President's Task Force on Regulatory Relief.

Two other divisions will also be streamlined. What is now the division of oncology and radiopharmaceutical

drugs will become oncologic and pulmonary drug products. Greg Burke, M.D., will be the acting director. The division of surgical and dental drug products will become radiopharmaceutical, surgical and dental drug products, headed by John Palmer, M.D., as acting director.

Steroid Traffickers Indicted

Two Florida men and four assistant coaches at the University of South Carolina have been charged in separate indictments with the illegal manufacture and distribution of both fake and genuine steroid drugs.

The Florida indictments, issued on April 17, charge Justin Rogers Routt and Clark Scott Daniels with operating clandestine laboratories in the South Miami area at which real and counterfeit steroid drugs were produced for illegal distribution. The men were thought to be the principal suppliers of illegal steroids in the Virginia, Maryland, and Washington, D.C., area as well as major suppliers of illegal steroids throughout Florida, the Southeast, and the Midwest. A search of Routt's laboratory and warehouse found \$2 million worth of bulk and finished steroid drugs and counterfeit products.

If convicted, Routt could be sentenced to 16 years in

prison and fined \$1 million. Daniels could receive 13 years in prison and a \$750,000 fine.

The South Carolina indictments, handed down April 19, involve three assistant football coaches and a strength and conditioning coach, all of whom are said to have promoted illegal use of steroids by athletes. Also indicted was John Landon Carter of Bethesda, Md. He was specifically charged with dispensing illegal steroids to a number of University of South Carolina football players.

USC assistant football coaches Thomas E. Gadd, James W. Washburn, and Thomas Kurucz were charged with conspiring to conduct a program of illegal steroid use among members of the university's football team. The strength and conditioning coach, Keith Kephart, was charged with conspiring with members of the USC athletic community to introduce illegal steroids into interstate commerce.

Steroid drugs are of limited use in some cases of breast cancer and in certain anemias. While they are being touted — especially among athletes and body builders — as a way to gain muscle mass, their misuse can cause severe physical problems, personality changes, and death. (For more on this, see "Athletes and Steroids: Playing a Deadly Game" in the November 1987 *FDA Consumer*.)

Revised "Orange Book" Available

FDA recently announced the availability of the ninth edition of *Approved Drug Products with Therapeutic Equivalence Evaluations* — better known as "the Orange Book."

This publication identifies prescription and certain nonprescription drug products approved by FDA. It also contains a section on therapeutic equivalence that compares generic drugs with approved multisource prescription drugs, a listing of approved orphan drugs, and patent and exclusivity information on drug products. The Orange Book is updated by monthly supplements.

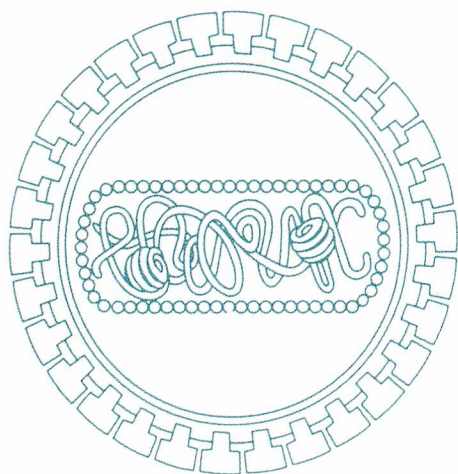
The publication, including supplements, is available for \$87 by subscription from the Government Printing Office (publication stock number 917-013-00000-4). Phone (202) 275-0019 for credit card orders (Choice, MasterCard, or Visa) or send a check to the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402-9371.

Correction: Publication Overpriced

Parts I and II of the *National Shellfish Sanitation Program Manual of Operations* cost \$10 each, not \$100, as stated in the May 1989 *FDA Consumer*.



Progress Reports in the Battle Against Acquired Immune Deficiency Syndrome



Safety Testing of GLQ223

Preliminary clinical testing of an experimental AIDS drug derived from a protein found in the Chinese cucumber plant was scheduled to begin in May at San Francisco General Hospital.

In April FDA approved an application from Genelabs Inc. of Redwood City, Calif., to study the safety of GLQ223 (also called Compound Q), a substance that has been shown in laboratory tests to inhibit reproduction of the AIDS virus.

GLQ223 is derived from a plant protein, trichosanthin, which is used in some Chinese herbal remedies. FDA and Genelabs caution, however, that the use of these remedies to treat AIDS could pose a serious risk to patients. Until the safety of the plant protein and of GLQ223 are known, indiscriminate use of these herbal remedies should be avoided.

Steady Climb in AIDS Products Approved for Clinical Studies

As of March 1, FDA had approved nearly 90 percent of 255 requests to study AIDS-related products in humans. Of the 224 IND (investigational new drug) approvals, 46 were for anti-viral drugs, 70 were for agents to affect immune function, six were for anti-cancer drugs, and 49 were for drugs to treat infections associated with AIDS. In addition, INDs were

approved for six AIDS vaccines and 49 diagnostic products.

In congressional testimony on FDA's budget request for fiscal year 1990, which begins Oct. 1, Commissioner Frank E. Young, M.D., Ph.D., said applications to carry out clinical trials of products to prevent, diagnose or treat AIDS and related conditions will reach 350 by year's end and may top 500 by the end of 1990. FDA receives about 10 applications a month for clinical testing of AIDS products.

Workshop on Community Based AIDS Drug Research

FDA headquarters and field staff presented a workshop on community-based AIDS research to tell researchers about the agency's review processes and how they can play a part in the development of AIDS drugs. Held at FDA's Rockville, Md., headquarters in mid-April, the workshop was part of an effort by FDA, the National Institute of Allergy and Infectious Diseases, and the Public Health Service to promote well-designed and well-conducted trials of potential AIDS therapies and to broaden patient and community involvement in drug development. (See "AIDS Research Comes to Patients' Home Towns" in the May 1989 FDA Consumer.)

In Day-Care Centers, Cleanliness Is a Must



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

Day-care centers have become a way of life in America. More than half of all mothers of children too young to care for themselves hold jobs outside the home. For them—indeed for millions of American families—day-care centers provide a service that is a necessity. If both parents work, a sole parent caring for a child must work, or other family support systems are inadequate, child day care answers a critical need. Unfortunately, though, it often provides something else—a focal point for certain kinds of infectious diseases that can all too easily spread not only to others in the day-care center, but far and wide into the community.

The problem involves illnesses, particularly enteric (small intestine) infections, that usually show themselves as diarrhea and other disturbances in the gastrointestinal tract.

Enteric illnesses are commonly associated with “food poisoning.” But in the nation’s day-care centers, tainted food is often not the culprit. Rather, the illnesses most often result from fecal contamination because staff and children fail to follow the dictates of ordinary common sense about things like hand washing and cleanliness.

The major contributors to the spread of enteric diseases—person-to-person contact, water and food—are interrelated and part of a persistent cycle. Attacking one part of the problem will have little effect. What’s needed is a concerted effort directed at all sources of transmission of enteric pathogens.

Studies show that children under 3 who are cared for in day-

care centers are more subject to diarrheal attacks than other youngsters. Likewise, day-care center workers and families of these young day-care children seem to suffer more bouts of diarrhea. L. K. Pickering, M.D., a professor of pediatrics at the University of Texas, noted in an editorial in the *American Journal of Public Health* that diarrhea was 30 percent more common in day-care children than in children cared for at home.

Another study found that day-care children under 3 had diarrhea twice as often as children remaining at home. A study reported in the September 1988 journal *Pediatrics* found an average of 3.8 diarrhea outbreaks per child per year in day-care centers in Houston, Texas. Similar findings have been reported from cities throughout the United States.

A recent family survey by Pickering and his colleagues showed that the average head of household or spouse lost 13 workdays because of illness in his or her day-care-center child; just under five of those lost days were due to diarrheal disease.

The spread of enteric illnesses to family members is documented in several surveys, one of which found that 10 of 56 family members of ill children were afflicted but only 1 of 45 family members of well children developed the illness. The episodes can be quite severe. One study reported a median duration of 12 days, while another noted that episodes lasted as long as six weeks. Hospitalizations were not all that infrequent.

The cause of these infections is usually some well-known pathogen such as the hepatitis A virus, rotavirus, *Giardia*, *E. coli*, *Cryptosporidium*, *Shigella*, or *Campylobacter*.

(Continued on next page)

The human gut, including that of small children, normally contains many of the pathogenic bacteria and viruses that can cause diarrhea, but the body's natural defenses usually keep them well under control. More important, these potentially dangerous organisms don't ordinarily get spread around. But fecal contamination can be a prime source of disease in centers that care for children under 3—those still in diapers and still being toilet trained. Hands, toys, diaper-changing areas, and just about everything else can be contaminated with fecal matter. Children and adults who touch these contaminated objects and then put their fingers to their mouths are prime candidates for disease.

A microbiologist in FDA's Center for Food Safety and Applied Nutrition, writing in the January/February 1989 issue of the *Journal of Environmental Health*, cautioned that diarrhea may not be the only consequence of fecal contamination in day-care centers. Noting that children generally have symptoms far longer than adults, he commented that diarrhea persisting a week or more can lead to nutrient losses and can also compromise the immune system. Further, in an important reminder that all of us should heed, he pointed out that both a form of arthritis and certain neuromuscular disorders have been associated with bacteria that cause diarrhea. And he reported the disquieting fact that some of the strains of pathogens causing outbreaks of diarrheal disease are extremely resistant to commonly used disinfectants.

Nevertheless, there are things day-care centers can do to minimize the danger of infection caused by fecal contamination. Preventive measures include:

- Hand washing. As simple as it may seem, hand washing is, as Professor Pickering says, "the single most preventive measure in the day-care center." Indeed, one study showed that outbreaks could be cut in half simply by requiring staff and children to wash their hands after diaper changes and bowel movements;
- Providing separate diaper-changing areas, preferably with disposable cover sheets and smooth, nonabsorbent, easily cleaned surfaces;
- Cleaning and disinfecting the diapering area after each use;
- Keeping younger children—especially those in diapers—separate from older children during the day;
- Keeping children with diarrhea at home;
- Segregating children whose diarrhea has stopped but who may still be carriers;
- Providing staff education on preventive measures and regular follow-ups to be sure the measures are being taken.

The U.S. Centers for Disease Control describes proper hand washing as follows:

- Use soap and running water.
- Rub your hands vigorously as you wash them.
- Wash all surfaces (including backs of hands; wrists, between fingers, and under fingernails).
- Rinse well and leave the water running.
- Dry hands with a single-use towel.
- Turn off water using a paper towel covering freshly washed hands.

Day-care staff members should wash their hands when they start work, before preparing or serving food, after diapering a child or wiping his nose or cleaning up messes, and after a trip to the bathroom.

For children, the routine is much the same, CDC advises. Center staff should be sure that children's hands are washed when they arrive, before they eat or drink, and after they use the toilet or have their diapers changed.

It's also important that the diaper-changing area is located well away from food-serving areas and that a separate sink is used for preparing food and washing dishes.

CDC recommends that only washable, preferably hard-surfaced toys be used around children still in diapers. Toys should be washed daily. Stuffed toys, if they're used by children in diapers, should be washed at least once a week.

Obviously, the need for cleanliness is not limited to hands and playthings. All facilities and supplies at day-care centers should be washed with soap and water and then disinfected on a regular, frequent schedule. For disinfectants, CDC recommends either a commercial product that kills bacteria, viruses, and parasites such as *Giardia* or a bleach solution. To make the bleach solution, mix one-fourth cup of bleach with a gallon of water (or one tablespoon per quart). The solution should be made daily but can be stored in a spray bottle. *Disinfectants must be kept out of the reach of children.*

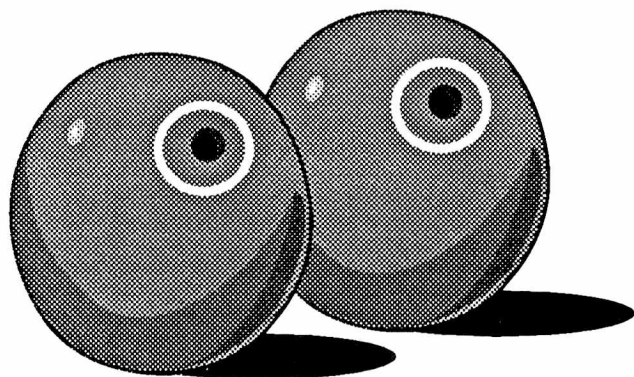
Any parent knows how disagreeable even a short bout of diarrhea can be in a young child. But public health workers know that diseases spread from day-care centers can have further, more ominous consequences. A day-care center child who contracts hepatitis A, for example, will probably develop only mild symptoms or none at all. Spread to adult family members, however, the infection carries the risk of more serious illness, as well as the possibility of further transmission to the community, particularly if the adult handles or prepares food. According to the National Restaurant Association, there are 8 million food service workers in 550,000 establishments in this country. It is easy to see how enteric disease in a day-care center child can have far-reaching effects into a wider world. In two studies, 13 percent to 40 percent of reported cases of hepatitis A in the community had some form of association with outbreaks in day-care centers.

FDA has model sanitation and food protection codes to which commercial food establishments must adhere. These same codes should apply to day-care centers that handle food, even though centers are not regulated by FDA. At FDA's urging, the National Environmental Health Association devoted its 1987 annual mid-year conference to day-care problems, particularly those associated with food protection and sanitation. The agency also recently signed a memorandum of understanding with the Department of Health and Human Service's Head Start Bureau. It provides for increased cooperation between Head Start and FDA's Center for Food Safety and Applied Nutrition to ensure that day-care centers follow standard sanitation and food protection requirements. And FDA continues to work closely with local and state regulators of day-care centers who are responsible for inspecting these facilities to help ensure that standard public health guidelines are being met.

My advice to parents of day-care center toddlers is: Make sure the day-care center is on guard against contamination that can make your child, you, and lots of other people needlessly sick. The risk is not just a bout of diarrhea. The risk is serious health problems down the road that can—and should—be prevented. ■

THE CYANIDE SCARE

A Tale of Two Grapes



by Bill Grigg and Vern Modeland

March 1989 marked the most intensive food safety investigation in Food and Drug Administration history. Millions of tons of fruit became suspect when a terrorist, 6,000 miles away, apparently made good on a phone call threatening to poison this nation's fresh fruit supply. Fruit in stores was returned or destroyed, and shipments coming into the country from Chile were halted.

In Chile, seasonable fruit and vegetable exports are second in importance only to copper to the national economy. In the United States, the cost of the terrorist's call might reach \$50 million—the estimated value of 45 million crates of nectarines, plums, peaches, apples, pears, raspberries, strawberries, blueberries, and table grapes that faced destruction.

How did it happen?

* * *

Since it was his turn as duty officer, Dick Swanson wasn't surprised when the black box on his belt beeped at 7:20 p.m., Friday, March 3. But the caller would have

to wait. Swanson was inside his van in the middle of the Potomac River. His van was one of eight or 10 cars jammed onto White's Ferry, guided by a cable across a bridgeless strip of river west of Washington.

Swanson, director of the Division of Emergency and Epidemiological Operations at FDA's headquarters in Rockville, Md., was minutes from his Virginia home and dinner. For a Friday, he had been thinking, he wasn't so late.

Ever since the 1982 Tylenol tampering crisis, his wife only half counted on him on Fridays. There always seemed to be emergencies at the end of a week.

A second beep sounded as he reached his door, so he headed straight to the telephone and called the number that had appeared on the beeper. A U.S. Customs official came on the line. He told Swanson that a cable from the U.S. Embassy in Santiago, Chile, had informed Customs:

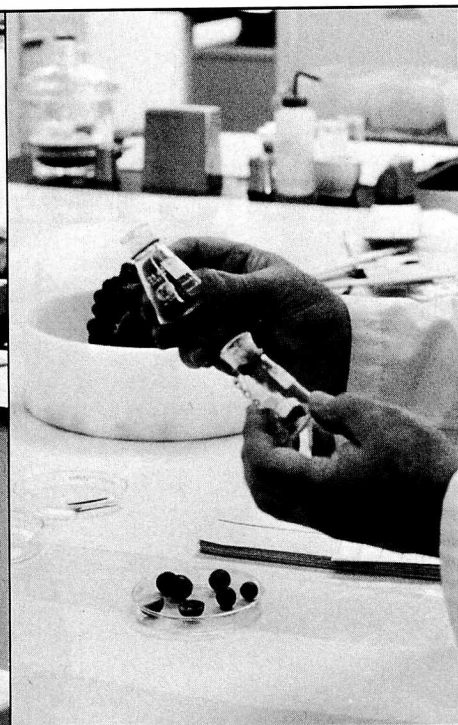
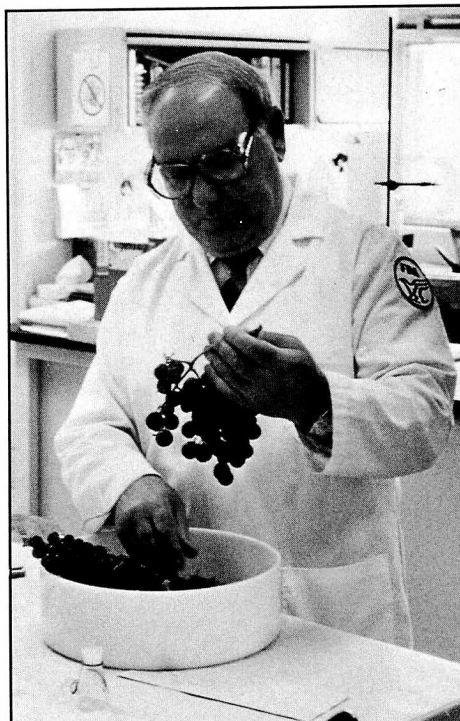
ON MARCH 2 AT 1550 HOURS AN EMPLOYEE OF THE AGRICULTURE PUBLIC HEALTH INSPECTION SERVICE RECEIVED A CALL FROM A SPANISH SPEAKING MAN, WHO SOUNDED MIDDLE AGED AND

WHO SPOKE WITH AN UNEDUCATED ACCENT. THE MAN STATED THAT FRUIT BEING EXPORTED TO BOTH THE UNITED STATES AND JAPAN WILL BE INJECTED WITH CYANIDE . . . IN ORDER TO FOCUS ATTENTION ON THE LIVING CONDITIONS OF THE LOWER CLASSES IN CHILE. HE FURTHER STATED THAT TOO MANY PEOPLE IN THE COUNTRYSIDE WERE STARVING DUE TO INCREASED LIVING COSTS AND WERE UNABLE TO BUY SUFFICIENT FOOD TO SURVIVE.

The caller said killing policemen and placing bombs had not solved the problem and he wanted to involve other countries. Although the Manuel Rodriguez Patriotic Front and the Leftist Revolutionary Front had been attacking policemen and placing bombs to bring about changes in the country and government of Augusto Pinochet, the caller did not say if he was involved with either group.

Swanson didn't get to the dinner table. He began a series of calls—to the commissioner, the deputy commissioner, and other headquarters executives. Swanson and

The evidence of tampering was there — two grapes had holes in them and contained cyanide. What was to be done about all the rest of the Chilean fruit?



Above, left: Nicholas Falcone, research coordinator in FDA's Philadelphia district, examines grapes from Chile. At the peak of the tampering crisis, the Philadelphia laboratory was performing 150 inspections a day.

At right, Falcone prepares suspicious grapes for a test to detect as little as 10-millionths of a gram of cyanide.

Richard Dees, investigations branch chief in the division of field investigations, then divided up the names of key field personnel, called them, and filled them in. "This is a Stage I alert. Customs has received a cable from State about a threat that poison will be put in fruit," they began. Swanson also called his counterpart in Canada, since Chilean fruit that enters the United States may wind up there.

Saturday, FDA Commissioner Frank E. Young, M.D., Ph.D., and others met at FDA headquarters in Rockville. They continued to confer on Sunday. But by Monday, the State Department had concluded the telephone call was "probably a hoax." FDA then released news of the call and State's view of it as a likely hoax. FDA said fruit had been temporarily held but was moving again. Few newspapers reported FDA's announcement. The crisis appeared over.

* * *

The terrorist called the embassy in Santiago again on the eighth of March, and again on March 17, warning that the March 2 threat was no hoax.

FDA began to step up inspections, mostly at the Port of Philadelphia, where 80 percent of all Chilean fruit imported by the United States arrives.

"We didn't know what kind of fruit had been targeted for poisoning or which ship would be carrying it. We set up a sampling schedule and went to work on the docks looking for it," says Richard Davis, regional food and drug director in Philadelphia.

First to be inspected would be the *Almeria Star*, which had sailed Feb. 27 from Santiago with 364,000 boxes of fruit in her holds. On Sunday, March 12, investigators began examining a representative 12,000 boxes of the fruit. While they worked, the *Mikawa Maru* and the *Reefer Jambu* waited in the Delaware River, carrying another 600,000 boxes of Chilean fruit. More was coming—as of March 16, 1.4 million tons was enroute.

To examine the growing mountain of Chilean fruit, the FDA Philadelphia district office needed extra help. Among

those assigned to the temporary duty was William T. Fidurski, from FDA's North Brunswick, N.J., resident inspection post. He was one of some 40 FDA people assigned to inspect fruit at the Tioga Fruit Terminal in Philadelphia.

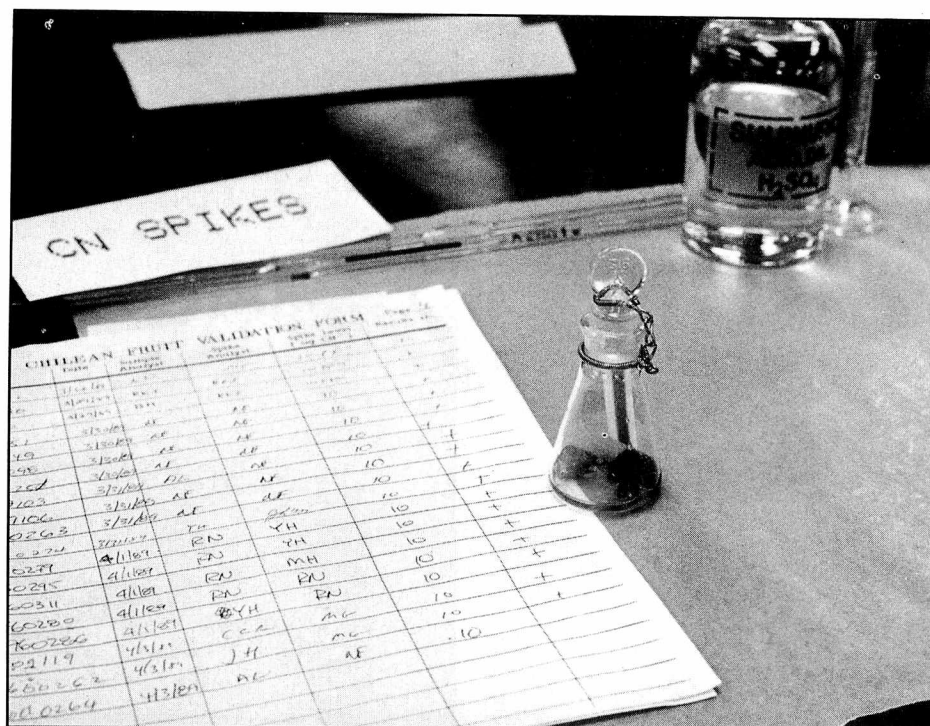
FDA investigators and trade association employees first would open the boxes picked at random from the consignment, then Fidurski and the other inspectors would take one and move it to their inspection area.

Protective plastic and paper wrappers, which looked intact, were carefully peeled back to expose the fruit to view.

"They were right on top of the box," Fidurski recalls. The red seedless grapes were discolored. They had damaged skins. That's about all he remembered about them, out of the 2 million grapes FDA investigators saw that day.

Being careful not to disturb anything in the box, Fidurski turned the crate over to his supervisor. It went, among others with damage or containing discolored fruit, to the FDA Philadelphia laboratory for closer

Room 1001 in the U.S. Customhouse in Philadelphia became, as a hand-lettered sign beside its door proclaimed, the "War Room" for three weeks.



"CN Spikes" reads the label above a log of test results on fruit that has been injected, or "spiked," with cyanide (CN = cyanide ion). The results are used to verify the method used in detecting cyanide in grapes.

examination. There, colored photos were taken that showed rings of a crystalline substance surrounding what might be puncture sites. The grapes then were sliced carefully and placed in small glass flasks. In the flasks, the slices were squeezed with a glass rod to release juice, and a solution of diluted sulfuric acid was added. Sulfuric acid will cause chemical changes to cyanide compounds, releasing hydrogen cyanide gas. A small strip of paper, coated with a reagent that turns blue in the presence of hydrogen cyanide, was placed in each flask and the bottles were capped with glass stoppers. This "cyanosmo test" would detect the presence of as little as 10-millionths of a gram of cyanide. Within minutes, it did. The analysts then did a Chloramine T test, which produces a pink-purple color in a reactive solution. The second test confirmed results of the first.

Those two red grapes contained cyanide in amounts far too small to cause death, or even illness, to anyone eating them. And, because crystalline potassium cyanide and sodium cyanide change to hydrogen cyanide gas in acid fruit and can then dissipate, FDA scientists couldn't determine how much of the poison might have origi-

nally been injected into the grapes. But, cyanide was present.

Back home, after his weekend of looking at fruit, Fidurski heard on a television newscast that FDA had found two grapes that contained cyanide. He immediately recognized the description.

In the hours between when Fidurski had noticed those damaged grapes and when he heard of them again on the television news from New York, the pressure on decision-makers grew.

* * *

Five men and a woman clustered around a speakerphone in the FDA commissioner's office, once again going over the same questions the world would soon be asking: Can we be sure it's cyanide? Should we act on two grapes? What if we don't? Is there more poisoned Chilean fruit on the *Almeria Star* — or on the many other ships waiting to unload or enroute from Chile?

On the other end of the telephone line was Frederick L. Fricke, FDA's preeminent expert on cyanide. "There were just two grapes found with cyanide, Fred," Com-

missioner Young said. "Very low levels. Very low . . . 0.003 milligrams vs. 20 to hurt an adult. Are you confident that the results are right—the cyanide was there?"

"Confident? Yes. The analysts [at the Philadelphia lab] are experienced with cyanide. They smelled cyanide [a "burnt almond" smell]. They confirmed it with two tests. The cyanide was low—maybe most had come back out the injection holes, or the acidity had dissipated it—but it was there. There was no reason to believe it was not there," said Fricke from his office in Cincinnati.

"I wanted to hear that from you," Young said, "because two grapes—that isn't much, people are going to say."

"Two grapes," FDA's associate commissioner for regulatory affairs John Taylor said. "They may kill us for reacting to two grapes. But I can't see we have much choice."

"There may be more we haven't found," someone said.

"The threat was not just grapes . . . 'fruit.'"

"We have to report what we've found, that's the minimum."

"Canada wanted to bar all Chilean fruit

Nationwide, by April 4, 7.9 million cases of Chilean fruit—including 6.1 million of grapes—had been processed and released.



In a mammoth Holt Terminal warehouse, on the docks at Camden, N.J., across the Delaware River from Philadelphia, approximately 100 FDA-trained inspectors examine green grapes from Chile, box by box by box.

imports just on the basis of the first threat. You know they'll bar it now."

"Where does that leave us?"

Young said, "I think we have to detain the fruit, at least until we know more. Kay [Hamric—Dr. Young's staff assistant], can you get me Dr. Mason and Dr. Sullivan?"

The newly confirmed Secretary of Health and Human Services, Louis W. Sullivan, M.D., and James O. Mason, M.D., assistant secretary for health, were quickly briefed. The many political and financial ramifications of a quarantine were discussed. Dr. Sullivan and his aides asked if there were any less drastic actions that could be taken. However, they agreed that HHS and FDA weren't charged with foreign policy considerations and commerce. "Our job," Sullivan said, "is the health of the American people."

A news release was drafted, in case it was needed. Copies were passed around the table and quickly approved: "The Food and Drug Administration said today it has found and confirmed traces of cyanide in a small sample of seedless red grapes from Chile and, as a result, is detaining all grapes and other fruit from

that country . . ."

On the evening newscasts March 13, much of the nation learned for the first time that most of the fresh fruit they enjoyed in the winter came from Chile.

* * *

In the Philadelphia Customhouse, the rest of that Sunday was spent testing all the other grapes packed in the same box where the cyanide-positive samples were found. FDA investigators looked carefully at the way the grapes were packed. They examined sulfate-impregnated pads placed with the grapes to retard spoilage, the wrapping paper around each bunch of grapes, the plastic box liner, and the box itself. Nothing extraordinary was found—no indications of tampering with anything other than the tainted grapes themselves.

Still, the evidence of tampering was there—two grapes had holes in them and contained cyanide. What was to be done about all the rest of the Chilean fruit?

* * *

It was obvious to one passenger in the no-longer-new compact car that Commissioner Young was a man of faith. The evidence was partly in the church program on the back seat—and largely in the way Dr. Young drove on a busy parkway toward downtown Washington while talking on his car phone . . . to Public Health Service executives, to Secretary Sullivan's staff, to the Chilean embassy, and to others.

But when Young arrived at FDA's downtown Washington building, the news wasn't good. Representatives of the importers and exporters were proving hard-nosed. "They're saying they can do a 1 or 2 percent inspection," a tired John Taylor told Young after a negotiation session. "That's no more than we were doing in Philadelphia before we found the grapes!"

Young and Taylor began to prepare a plan for 5 percent inspections to be carried out by food graders, paid for by industry, but trained, supervised and audited by FDA. (FDA, with only 1,000 investigators nationwide, couldn't handle the job itself and still cover blood banks, drug companies, warehouses, and all the other facilities requiring checks.)



Getting Cyanide into Fruit Is Not So Easy

Scientists at FDA's Center for Food Safety and Applied Nutrition are investigating how susceptible fruit is to injection with cyanide and are discovering some things consumers may find worth knowing:

- Although there is variation among fruit, injecting fruit with enough cyanide to hurt or kill isn't quite as easy as it sounds. In some cases, some of the poison may leak back out of the injection hole or, in others, it may be dissipated by chemical reaction with the acidity of the fruit. It's also hard to inject some fruit, such as plums. Preparing or carrying cyanide in a form and strength to render fruit harmful can be dangerous to a would-be tamperer or terrorist, who might injure or kill himself.
- There are some signs the purchaser can watch for. The chemical reactions that occur may discolor fruit, causing it to look blemished, bruised or overripe. Consumers can examine fruit for these signs as well as for injection holes. The grapes found in Philadelphia also had rings of a white residue, presumably from the injected material, around the injection sites.

This is what could get the fruit moving again, they told the industry.

With any number of details still to be worked out and agreed to, Sullivan and Young announced on March 17—five days after the detention began—the gradual return of Chilean fruit.

* * *

The next day in Philadelphia, FDA investigators began training the first group of food graders in what to look for. That afternoon, inspections at the 5 percent level began.

Room 1001 in the U.S. Customhouse in downtown Philadelphia became, as a hand-lettered sign beside its door proclaimed, the "War Room" for the next three weeks. Taped to the door itself was one of the colored photos taken of the red grapes. Someone had added a hand-lettered description: "The Enemy."

At the peak of the crisis, 15 percent of the entire FDA inspection force became involved in examining Chilean fruit. They came from as far away as Minneapolis and San Juan, expanding the inspection team working out of Philadelphia to 166 at

one time.

In FDA's Philadelphia district laboratories, on the 11th floor of the Customhouse, analysis of suspicious fruit peaked at 150 samples a day. And, while they worked, the analysts could easily be intimidated by a glance out of their windows toward the Delaware River. For a time, five refrigerated freighters loaded with Chilean fruit were anchored in mid-river, awaiting dock space as the intensified inspections slowed unloading.

Since entire shipments were held in quarantine while representative samples were examined, cold storage sites around Philadelphia filled quickly. Grocers were adding to the strain on refrigerated storage capacity as they returned fruit they had removed from sale. FDA's investigators found it necessary to cover an ever-widening area in keeping track of the mountain of fruit that was suddenly of so much interest to so many.

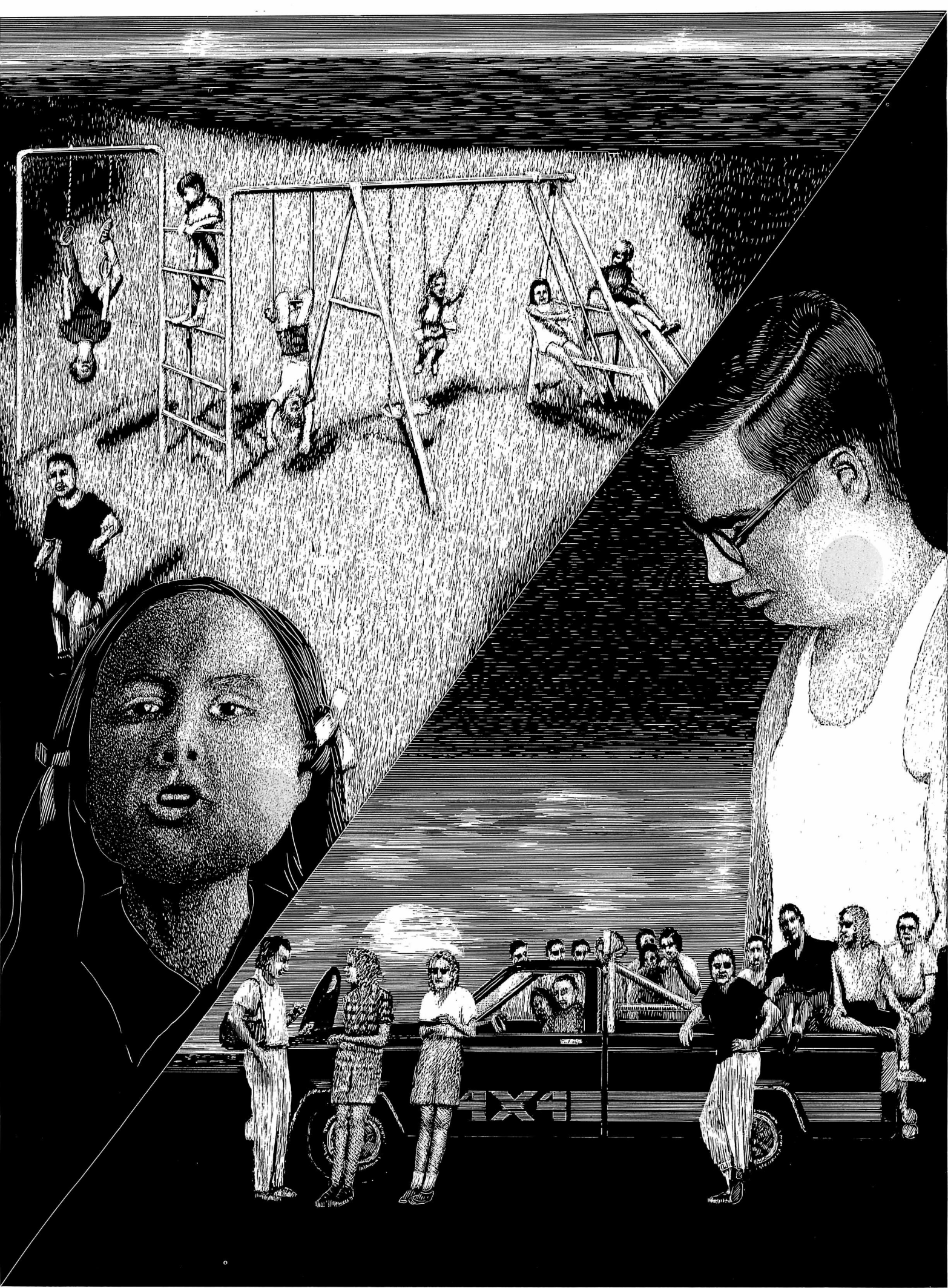
By April 4, 4,781,361 cases of Chilean fruit had been processed and released at the Philadelphia area examination sites. Nationwide, the total was closer to 7.9 million cases, including 6.1 million crates of grapes, as the inspection activity also

peaked in Miami and Los Angeles, the other major ports of entry for fruit from Chile destined for American consumers. FDA lowered its level of inspection to 4 percent on March 27, then to 1 percent on April 6. By the end of the crisis, on April 14, when Chilean authorities assumed the inspection responsibility in their country, more than 9 million crates of Chilean fruit had been marked "inspected and cleared."

"This has been a difficult time," FDA Commissioner Young reflected as the fruit reappeared on produce counters. He praised the Chilean efforts at greater security and said that this—together with greater consumer awareness, better understanding of the chemistry involved, and the fact that no additional signs of tampering had been found—permitted a return to normal.

At a Chilean embassy party in Washington, D.C., among those in the brown bag lunch bunch at FDA, and in homes across America, people were eating grapes again. ■

Bill Grigg is director of FDA's press office. Vern Modeland is a member of the agency's public affairs staff.



MUMPS

MAKES A COMEBACK

by Judith Levine Willis

It was the second week of October 1987. The Chicago futures exchange was a hive of hyperactivity, so crowded and noisy that the traders had to shout out their buy and sell orders right into each other's faces. By Oct. 19, the futures flurry had turned into an epidemic of stock selling that plunged the market into a crash. At the futures exchange, though, the activity had had still another effect—it brought to a peak an outbreak of mumps that had begun the preceding August.

Three futures exchanges were involved in the outbreak that saw 116 employees (and three of their family members) with clinically diagnosed cases of mumps before the outbreak ended in December. Mumps is contracted by person-to-person contact with droplets from the nose, throat or saliva of someone infected with the mumps virus. (Mumps is not as easily transmitted as measles—see accompanying article.) The Centers for Disease Control speculates that this outbreak peaked at the time of intense activity on the exchanges because the crowded conditions and feverish bidding made contact with an infected person's sputum more likely. Spread of the disease was probably further accelerated by the dedication of some employees who, because of the unusual pressures at the time, came to work despite such symptoms as the low to moderate fever that often precedes facial swelling around the jaw. In addition, mumps is most infectious during the 48 hours before clinical symptoms appear.

Unwelcome Guest

But what was mumps, a "childhood disease," doing visiting the very adult

Chicago futures exchanges in the first place? Because vaccination was available in 1967 but was not widely used in this country until 1977, there is now a population of young adults who may be susceptible to the disease. Thus, while mumps is now rare in elementary school children, it is making inroads among those in their teens and 20s. At the Chicago exchanges, though ages of those who had clinical cases of mumps were from 17 to 70, persons younger than 30 accounted for 77 percent of the cases. More than a third of the 82 patients for whom information was available believed they had previously been vaccinated, but only three of them could provide vaccination records.

It is likely that more than 116 persons were actually involved in this outbreak. Only about two-thirds of those infected with mumps get the facial or jaw swelling that people typically associate with mumps. (The swelling is caused by inflammation of the parotid, a salivary gland, and usually lasts two or more days.) In medical terminology, these people are said to have "clinical cases" of mumps. The remaining third have no symptoms at all or symptoms, such as a low-grade fever, that would not be readily identified as mumps. Though these people probably would not be diagnosed as having the disease, they nevertheless have subclinical cases and are capable of spreading it. They also acquire lifelong immunity, along with those who have diagnosable symptoms.

Complications

Complications of mumps in people past puberty are often more serious than those in children. Of the employees with diag-

nosable symptoms, 15 men had inflammation of the testes and sperm duct, four of them requiring hospitalization. One woman had inflamed ovaries and another, who was pregnant, went into premature labor that was later arrested. Other complications of the illness included arthritis, meningitis, inflammation of the pancreas, and inflammation of the parotid gland severe enough for hospitalization.

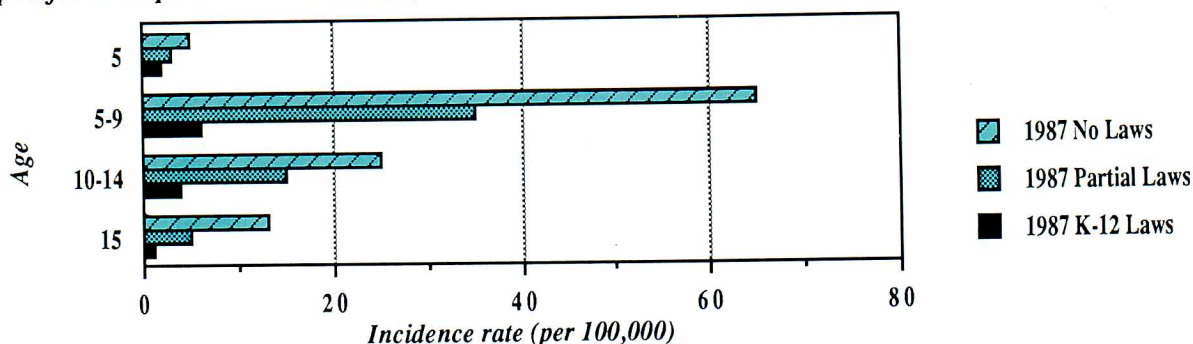
In cooperation with CDC, the futures exchanges sponsored voluntary vaccination clinics for employees in November 1987. Though cases continued occurring into December, many, if not most, of these employees were probably infected before the vaccination program, as the incubation period for mumps, though usually 16 to 18 days, can range from 12 to 25 days.

The Chicago outbreak is by no means an isolated instance of mumps among young adults. CDC reports a number of outbreaks in high schools and on college campuses. In 1986–87, CDC investigated outbreaks of mumps at three Illinois colleges, five colleges in South Dakota, and one in Wisconsin. In these and other outbreaks among teens and young adults, CDC has observed that 20 percent to 30 percent of the males develop inflamed testes and sperm ducts that may, in rare cases, cause sterility. Up to 60 percent of the young people may develop abnormalities in cerebrospinal fluid usually associated with viral meningitis, while 10 percent actually develop overt signs of brain inflammation, characterized by fever, headache, and neck stiffness.

Though not a factor in these college outbreaks, there is a high risk of miscarriage

(continued on page 16)

Age-specific mumps incidence rates, by school immunization law status —United States, 1987



Mumps Facts

Medical name: epidemic parotitis

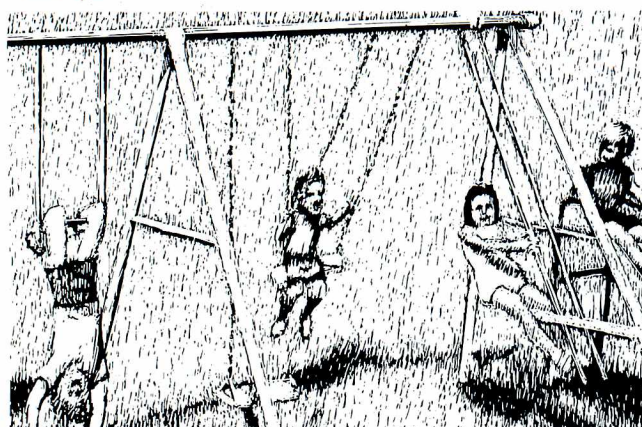
Transmission: moderately easy by person-to-person contact with droplets from the nose, throat, or mouth of a person infected with the mumps virus.

Incubation period: 12 to 25 days, but usually 16 to 18 days

Symptoms: *at onset:* chills, headache, loss of appetite, malaise, low to moderate fever 12 to 24 hours before swelling of salivary (parotid) gland, pain upon chewing or swallowing (especially with acidic liquids such as vinegar or lemon juice), sensitivity to pressure at jawline; *fully developed disease:* gland swelling accompanied by fever rising to 103 to 104 degrees Fahrenheit.

Possible complications: involvement of organs other than salivary glands, especially in persons past puberty. Inflammation of testes and sperm ducts in 20 percent to 30 percent of postpubertal males, but sterility is rare; inflammation of ovaries in a lesser percentage of postpubertal females, not associated with infertility. Symptoms of viral meningitis, such as fever and stiff neck, are common and become severe in 5 percent to 10 percent of cases (about 30 percent of persons with such symptoms do not have parotid gland swelling).

Prevention: immunization for persons born after 1956. Babies should be vaccinated with MMR (measles, mumps, rubella) at 15 months of age and again before entering school. ■



Measles Facts

Medical name: rubeola

Transmission: extremely easy from contact with microscopic airborne droplets, or by direct contact with droplets from the nose, throat or mouth of a person infected with the measles virus.

Incubation period: 7 to 18 days

Symptoms: fever, runny nose, cough, conjunctivitis for two to four days before appearance of Koplik's spots (small red spots) inside cheeks. Inflamed throat and laryngitis may develop before outbreak of rash three to five days after initial symptoms (one to two days after Koplik's spots). The rash begins on the face and side of the neck, and spreads to the trunk, arms and legs within 24 to 48 hours. Temperature may peak over 104 degrees Fahrenheit and sensitivity to light is common. Fever falls in three to five days, and the rash fades leaving coppery brown discoloration followed by peeling. Persons immunized only with the killed virus vaccine (which is no longer used) may develop atypical measles syndrome—an abrupt high fever, abdominal pain, and cough followed by a rash one to two days later, with pneumonia and swelling of hands and feet.

Possible complications: pneumonia, particularly in infants; middle ear and other bacterial infections, especially strep; blood abnormalities; encephalitis (1 in 600 to 1,000 cases); subacute sclerosing panencephalitis (SSPE), a rare and previously unexplained chronic fatal brain disease in children and adolescents occurring months to (more usually) years after measles.

Prevention: immunization with live attenuated (weakened) vaccine for persons born after 1956. Children should be vaccinated with MMR (measles, mumps, rubella) at 15 months of age and again before entering school, except for those in areas where there have been repeated measles outbreaks or where there is a current outbreak. In these areas, babies should receive measles vaccine at 9 months and the trivalent (MMR) vaccine at 15 months. (An alternative is a single dose of trivalent vaccine at 12 months of age.) In school outbreaks, persons vaccinated before 1980 and those who received the vaccine before 15 months of age should be revaccinated. ■



... And Measles, Too

Ken was the sickest his mother had ever seen him. At first it had seemed like just another throat infection and cough. The doctor had found strep (short for the bacterium *Streptococcus*) and prescribed ampicillin. But after two days of taking the antibiotic, the 12-year-old was still running a fever of 102 degrees Fahrenheit. In the next few days the fever continued to rise and Ken broke out in a rash. Thinking either scarlet fever or a drug reaction was responsible for the rash, the doctor switched Ken to another antibiotic. But the fever and rash persisted and Ken started complaining about "too much light." Once he even walked into a mirror.

"If he hadn't been immunized, I would think he had measles," his mom remarked, recalling her own battle with the disease in the '50s.

In this case, mother knew best. Several days later, after the fever had broken, a number of Ken's classmates reported similar symptoms, and the doctor—who had discounted measles because Ken had received his measles vaccination in 1977 when 16 months old—had to reevaluate his diagnosis.

This was just one of several measles outbreaks on this continent in the last few years. The most severe have been in Houston and Los Angeles.

Why Is This Happening?

Experts at the Centers for Disease Control say that it is not unusual for vaccinated persons to come down with the disease—in fact there have been measles outbreaks in high schools where every one of the students had been vaccinated, according to Bradley

S. Hersh of the CDC. He points out that vaccination does not always guarantee protection against disease. A small percentage of children vaccinated before 15 months of age may not acquire full immunity from the shot. And a small percentage of persons vaccinated before 1980 may have received ineffective vaccine because the vaccine used then sometimes weakened in light and heat. Since that time a new stabilizer that eliminates this problem has been used. The present vaccine is highly effective, conferring immunity in 95 percent of those who receive it. But, as Hersh points out, this means that 5 percent are not immune and "measles is good at picking people out of the crowd."

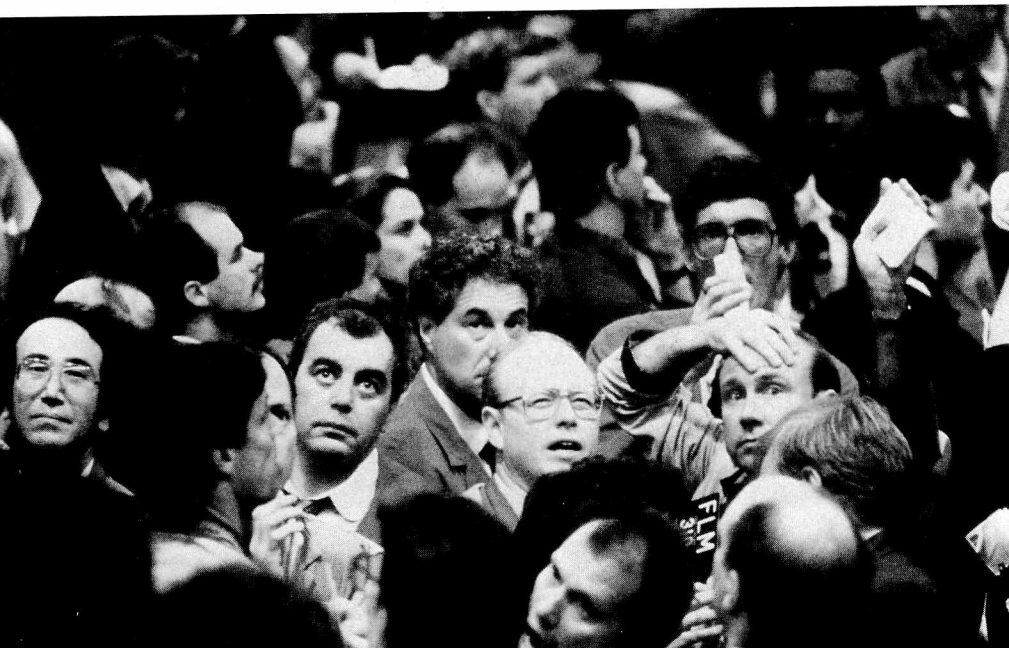
In the late 1970s, the medical community thought it would be able to eradicate measles here by 1982. This has turned out to be overly optimistic although there has been a dramatic reduction in the number of cases. In 1962, the year before the vaccine was developed, there were 500,000 cases of measles. After the vaccine was licensed, the number of cases decreased dramatically. The record low year was 1983, when fewer than 2,000 cases were reported.

Yet the disease refuses to die. In 1984, the incidence began to rise, with a peak outbreak year in 1986 of 6,286 reported cases. In 1988, there were 3,250 cases and CDC, monitoring early trends, thinks that the rates for 1989 may possibly be even higher than in 1986. Although current rates are still way below the pre-vaccine era and more than 95 percent of U.S. counties report no cases at all, the fact that measles persists is of concern. (See "Measles on the Rebound" in the October 1986 *FDA Consumer*.)

New Recommendations

After reviewing the current situation, the Public Health Service recently issued new recommendations for routine measles vaccination of infants in localities with recurrent measles outbreaks and for controlling school-based outbreaks. For infants, a two-dose schedule is recommended, with measles-only vaccine at 9 months of age and measles-mumps-rubella vaccine (MMR) at 15 months. (If resources do not permit two doses, an alternative is a single dose of MMR at 12 months of age.) In school outbreaks, for those who were vaccinated before 1980, PHS recommends revaccination for all students (and their siblings) who attend schools where there have been cases of measles or who might have contact with students from affected schools. (If this is impractical, then those vaccinated before 15 months of age should be revaccinated.)

For the general population, it is presumed that persons born before 1957 are immune. Those born after this date are advised to check their immunization records to make sure that they were vaccinated after the age of 15 months. Babies in communities where there are no measles cases should not be immunized until they are 15 months old, because immunization before that age is less likely to confer lifelong immunity. To further increase immunity in the general population, PHS recently recommended that children receive a second dose of MMR before entering school. ■



*Close quarters at the Chicago Mercantile Exchange during the frenzied trading of October 1987 encouraged transmission of mumps, bringing to a peak an outbreak in young adults that began that August.
(Photo by Steve Leonard, Black Star)*

(continued from page 13)

if a woman develops mumps in the first trimester of pregnancy.

Reason for Population Shift

The reason for this shift of mumps to an older age group can probably be traced to the history of immunization against childhood diseases in this country. A mumps vaccine was licensed in 1967, four years after licensing of the measles vaccine. However, because the mumps vaccine was more expensive and childhood mumps was perceived as a mild disease, mumps immunization was given lower priority than immunization to measles (rubeola) or German measles (rubella). The latter, though also a comparatively mild disease, nevertheless often causes birth defects if a woman is pregnant. The mumps vaccine was licensed in a combined vaccine with rubella in 1970, in a combined "trivalent" (containing three) vaccine with both measles and rubella in 1971, and in a combined vaccine with only measles in 1973. It is the second, "trivalent," combination (often abbreviated MMR) that continues to be most widely used today.

However, despite its availability, its use wasn't widespread until 1977, when, following recommendations by the Public Health Service, a number of states passed laws requiring immunizations for seven diseases—measles, mumps, rubella, diphtheria, pertussis, tetanus and polio—before a child could enter public school. Mumps vaccination of older children and young adults was not aggressively advocated until 1980.

Thus, there is a pool of young people

born between 1957 and 1977 who "fell through the cracks" between presumed immunity and immunity through vaccination. Those born before 1957 are presumed immune even if they did not get sick because the disease was so widespread. Those born between 1967 and 1977 grew up when the risk of exposure to mumps was rapidly declining as the vaccination of younger children became more common. They are now at higher risk of contracting mumps than those born the previous 10 years because there is more chance that persons born between 1957 and 1967 were exposed to the disease while young.

An additional problem is that requirements for immunization sometimes vary from state to state. According to CDC, a direct relationship exists between reported mumps incidence and school immunization laws. The more stringent the requirements for immunization, the lower the reported incidence of the disease. In the 14 states (and the District of Columbia) that require all schoolchildren to have proof of mumps immunity, the rate of mumps in 1987 was 1.1 per 100,000 persons. In 18 states with partial vaccination requirements that do not comprehensively include all children in kindergarten through twelfth grade, the rate was 6.2 per 100,000. In states lacking any immunization requirements, the rate was 11.5 per 100,000.

Due to this pattern, CDC believes the incidence in young adults is primarily related to lack of vaccination rather than to any failure of the vaccine to protect against mumps. Close watch is being kept over the incidence rates because of large jumps in

the number of cases in recent years. Following the institution of vaccination programs, the number of reported mumps cases steadily declined for a number of years, reaching a low of 2,982 cases in 1985. (This was a 98 percent decline from the 152,000 cases reported in 1968, the first year that mumps was required to be reported.) However, the rate rose to 7,790 in 1986 and then jumped to 12,848 cases in 1987. CDC is cautious about taking any comfort from the decline of the number of cases to 4,730 in 1988 because of the likelihood of underreporting and because of the continued outbreaks it has observed thus far in 1989.

What to Do

What should a person who's never had mumps do? Individuals born before 1957 need do nothing. Even if they've never had symptoms of mumps, they are presumed immune (assumed to have had subclinical infection and to have developed antibodies) due to universal childhood exposure at that time. However, in mumps outbreaks, persons born before 1957 who question their immunity may want to consider being vaccinated as a precaution. Persons born after 1956 should check vaccination records to determine if they've been immunized against mumps. If not, they should receive the measles-mumps-rubella (MMR) vaccine or other mumps vaccine as recommended by their physicians. ■

Judith Levine Willis is editor of the FDA Drug Bulletin, a publication for health professionals.



THE PUZZLING PICTURE OF MULTIPLE SCLEROSIS

by Margie Patlak

Neal Schmidtke of Waukesha, Wis., used to keep in shape by bounding up stairs two at a time and running to his appointments. But in January of 1987, when he was 31, Schmidtke started tiring quickly and feeling weak in the knees. By summer, clumsiness replaced his athletic prowess when he started having numbness in his hands and feet and frequent muscle twitches. Soon he could no longer shave or even stand in the shower. After blacking out a few times in August, Schmidtke embarked on a medical odyssey through four months of tests adding up to \$20,000 in doctor bills and a near-certain diagnosis of multiple sclerosis.

Each year, 8,000 Americans are told they have multiple sclerosis, a debilitating ailment whose cause and cure are unknown. Even diagnosing multiple sclerosis is difficult and fraught with uncertainties. Symptoms vary greatly among patients and, over time, even within a single individual. This variability stems from the very nature of the disease.

The symptoms of multiple sclerosis are due to patchy destruction of the fatty sheath, called myelin, that envelops and insulates the nerves in the brain and spinal column. Scar tissue forms wherever the myelin jacket is lost, causing a hardening, or "sclerosis." The scar tissue slows or blocks the passage of messages along these nerves, which govern body movements and permit sensations of temperature and pain, among others. Because different nerves service different parts of the body, symptoms of multiple sclerosis vary according to which nerves have myelin destruction. A patient whose sclerosis is mainly limited to the nerves controlling the limbs, for example, will have numbness and, in extreme cases, paralysis of the extremities, whereas another patient may suffer more from vision problems because the optic nerves are affected.

Some common symptoms of multiple sclerosis are weakness, tingling, numbness, loss of coordination and balance, dizziness, fatigue, impotence, muscle spasms, slurred speech, burning or painful sensations, and blind spots in the center of vision. Blurred or double vision is often the first sign of the disease; a common late symptom is loss of bowel and bladder control. Patients are spared any mental disabilities, except in rare instances.

Usually symptoms come and go mysteriously. Attacks (the occurrence or worsening of symptoms) are considered by many doctors to be a sign of myelin destruction, while remissions (ces-

(Continued on page 19)



Neal Schmidtke doesn't let his multiple sclerosis get in the way of sharing kitchen duty with his wife, Laurie, and daughter, Alissa.

(Reprinted from The Milwaukee Journal)

MS



(Continued from page 17)

sation or lessening of symptoms) are thought by some doctors to signify myelin repair, although this remains to be proven.

Most patients initially have a series of attacks followed by periods of complete or partial recovery. As years go by, the attacks become more frequent and there is less improvement during remissions until, in the late stages of disease, patients usually experience a progressive decline with no remissions.

Multiple sclerosis is rarely fatal; however, the average life expectancy of a patient is 93 percent of that of the general population. Nor is the disease always disabling; 1 out of 5 patients only has one attack, with little to no progression thereafter. Studies show that two-thirds of patients are still able to walk with or without the assistance of walking aids 25 years after their disease was diagnosed. Of those, at least half can engage in most of the activities they performed before developing the disorder for as long as 15 to 20 years after its onset. In a small percentage of patients, the disease progresses very rapidly and leads to premature death from disease complications such as pneumonia and other infections.

Tricky to Diagnose

Most of the nearly 500,000 American men and women diagnosed with multiple sclerosis first get symptoms between the ages of 20 and 50. Diagnosis is difficult and often slow because so many neurologic and other disorders cause some of the same symptoms seen with multiple sclerosis. A person who is having trouble in only one part of the central nervous system, for example, often has to undergo special X-ray tests to rule out other causes, particularly tumors and strokes.

Unsuspected patches of myelin destruction are sometimes detected in sensory evoked potential tests. These painless tests use electrodes attached to the skin to measure how quickly nerve messages travel from the eye, ear or skin to the brain.

Magnetic resonance imaging (MRI) can also locate demyelinated areas in the brain and spinal cord. The patient lies still for about a half hour in a large doughnut-shaped magnet, while the tissues are pulsed with radio waves. Radio signals emitted by diseased tissue differ from those of healthy tissue.

Spinal taps—in which a small sample of spinal fluid is drawn for analysis—are often done to measure the levels of certain antibodies and cells that are usually elevated in patients with multiple sclerosis.

The sporadic nature of the disease also makes it difficult to diagnose. For example, a person may have vision problems typical of multiple sclerosis, but not have the disease. Most such people never experience the problem more than once. Those with recurrences usually have multiple sclerosis, but another episode of vision disturbance may not surface for months or even years after the first. Often multiple sclerosis cannot be firmly diagnosed until a person has had at least two episodes of dysfunction involving more than one area of the central nervous system that cannot be otherwise explained.

The cause of myelin destruction in multiple sclerosis eludes scientists. The myelin seems to be under attack by the body's own immune system cells. Some studies show that white blood cells, for example, help break down myelin in these patients. But what misdirects these cells to attack rather than defend the nervous system is not known. Over the past 10 or 15 years, however, researchers have concentrated on some clues that should hasten a better understanding of the disorder.

A visually striking clue is a map of the prevalence of multiple sclerosis. Certain regions of the world with a temperate climate, such as the northern United States, Canada and Europe, have almost 10 times the number of multiple sclerosis cases as tropical

regions. Age also seems to be significant in terms of risk. Studies show that a person moving from a temperate climate to a tropical climate before the age of 15 tends to adopt the risk associated with the new area, whereas people who move after age 15 maintain the risk of their homeland.

Search for a Viral Cause

These findings suggest that some environmental factor could influence a person's risk for multiple sclerosis up to age 15. It could be a virus native to temperate regions that lies dormant in the body for years before some event triggers it. At least two other human neurological disorders are known to be caused by such "slow" viruses.

A virus could cause myelin loss by attacking the myelin or the cells that produce and maintain myelin. Or, if the molecular structure of the invading virus were identical to part of the molecular structure of myelin, the invader could provoke the immune system to attack both the virus and the myelin. Over the years, more than 20 different viruses have been suspected of being linked to multiple sclerosis.

Recently, the human T-lymphotropic virus (HTLV-I) has come to the forefront in the scientific search for the cause of multiple sclerosis. This virus has been linked to other nervous system disorders and to blood cancers. HTLV-I is a retrovirus, a kind of virus that uses an enzyme to convert its genetic material, RNA (ribonucleic acid), to DNA (deoxyribonucleic acid). The viral DNA then becomes integrated with the DNA of the host cell, where it may remain silent for years without causing symptoms. A research group at the Wistar Institute in Philadelphia has found pieces of genetic material nearly identical to that of HTLV-I in the blood cells of all six of the multiple sclerosis patients they've tested, but in only 1 of 20 people tested without the disorder. They also found particles that look like retroviruses under the electron microscope in tissue taken from one multiple sclerosis patient. Similar findings were generated by a research group at the National Cancer Institute in Bethesda, Md.

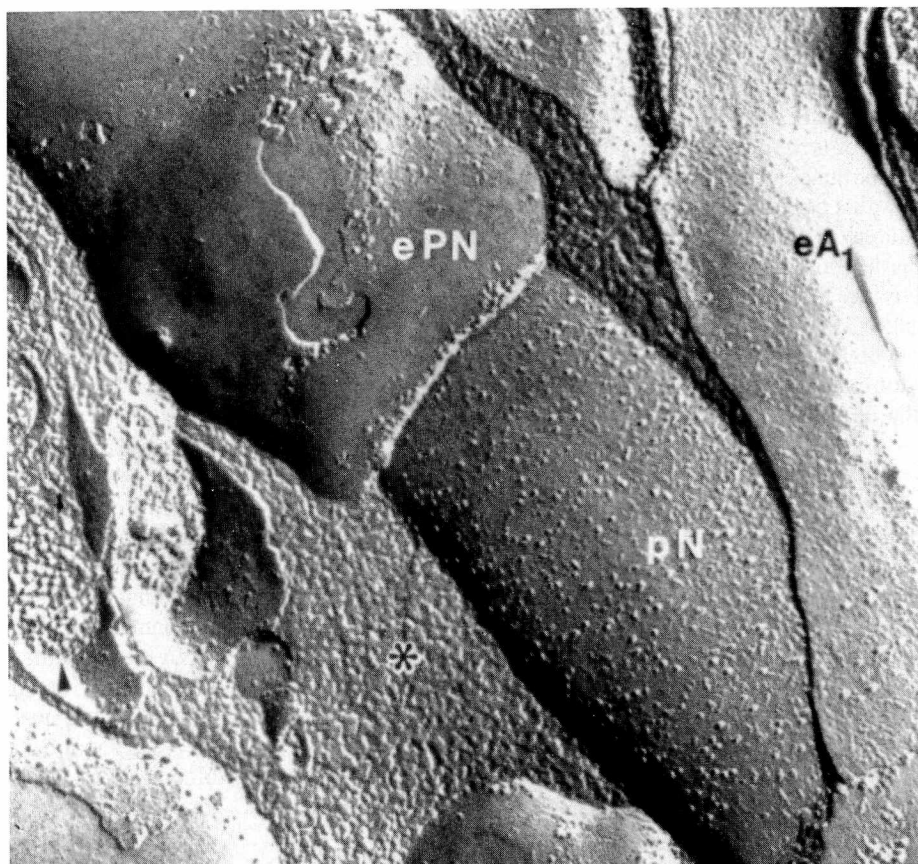
The presence of HTLV-I or a relative of it in the blood of multiple sclerosis patients doesn't necessarily mean the virus causes the disorder. "But before any of the retroviruses were found to cause disease in humans," says Dale McFarlin, M.D., a multiple sclerosis expert at the National Institute of Neurological and Communicative Disorders and Stroke, "we suspected that a retrovirus caused multiple sclerosis." Much more research is needed, he adds, however, before researchers will be able to conclude with certainty that HTLV-I or its relative sparks the development of the disease.

The Gene Scene

Meanwhile McFarlin and other researchers working on the genetic front have turned up two genes that, when inherited together, triple a person's risk of developing multiple sclerosis. Although multiple sclerosis is not considered an inherited disease, the chance of a parent or sibling of a patient also having the disorder is 10 to 15 times higher than that of the general population. The disease is thought to be caused, in part, by abnormalities in immune function, and scientists have been studying the genes that govern the immune system to find those that make a person more susceptible to the disease. One of the genes McFarlin has pinpointed prompts the production of a protein, called DR2, that juts out of the surface of white blood cells. DR2 is one of a myriad of proteins called HLA (human leukocyte antigen) molecules, whose various combinations give an individual "fingerprint" to each person's cells. Scientists suspect that the immune system relies on the HLA fingerprint to distinguish

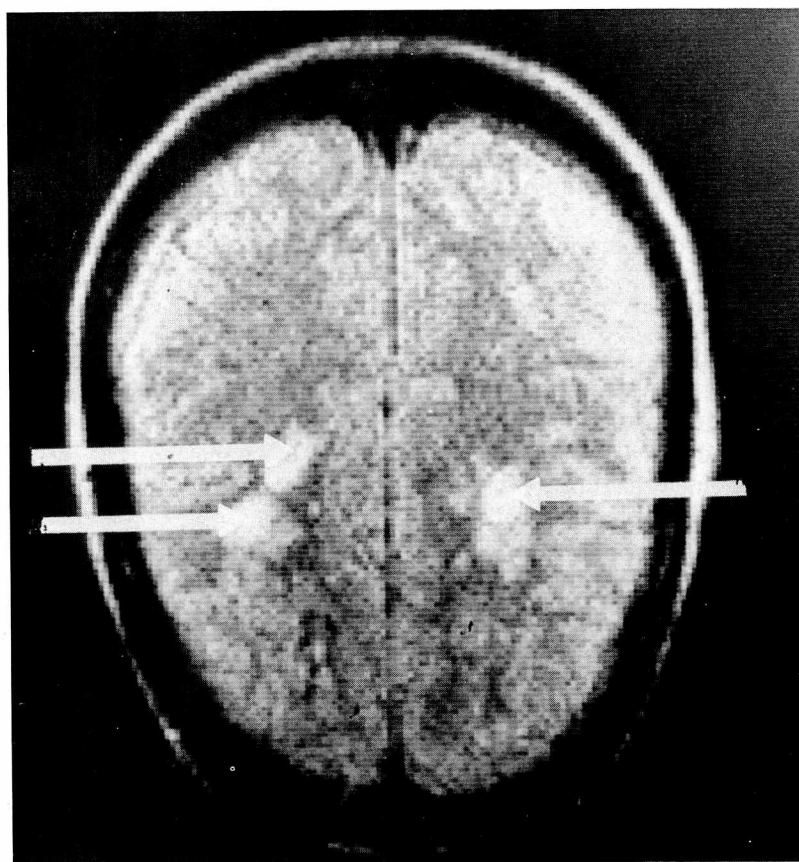
(Continued on page 21)

This electron micrograph shows a nerve fiber (pN)—magnified 48,000 times—“wrapped” by the myelin sheath (ePN). Astrocytes, a type of nerve cell (marked eA₁ on the photograph), proliferate and form the scars (sclerosis) in multiple sclerosis. (Photograph courtesy of Stephen G. Waxman, M.D., Yale University School of Medicine, New Haven, Conn.)



Magnetic resonance imaging scan of the brain of a patient with multiple sclerosis. The arrows point to lesions in white matter—tissue constituting the conducting portion of the brain and composed mostly of myelinated nerve fibers.

(Photo courtesy of Donald Paty, M.D., University of British Columbia, Vancouver, Canada)



(Continued from page 19)

between cells that are “self” and not to be destroyed and cells that are foreign and subject to attack.

Researchers were particularly interested in finding the gene that prompts the production of the DR2 protein because studies have shown that multiple sclerosis patients are more likely to have this subtype of DR2 protein than others, although the presence of DR2 does not necessarily mean a person will develop multiple sclerosis.

The other gene known to heighten susceptibility to multiple sclerosis governs the production of a receptor protein on the surface of a type of white blood cell called a T cell. The receptor is essential for the functioning of T cells, which orchestrate immune defenses. Other genes also probably play a role, McFarlin says. “A person would have to have just the right combination of several genes,” he says, “to be prone to multiple sclerosis, which would explain why the disease is so rare.”

It's not known yet how the genes that code for DR2 and the T cell receptor proteins boost the risk of developing multiple sclerosis. One possible scenario is that in a person who inherits these two genes as well as certain others, multiple sclerosis begins when a virus damages some myelin. The body's scavenger cells (macrophages) then digest the damaged myelin and in the process display myelin protein fragments in the grooves of the DR2 molecules dotting their surfaces. Patrolling T cells that would not normally bind to these self proteins do so in someone with the right genetic makeup, and prompt the destruction of other cells bearing the same protein fragments as well.

Although scientists don't know what causes multiple sclerosis, some of the pieces to the puzzle they've uncovered so far have fostered a number of experimental treatments. Researchers are testing these treatments to see if they can stave off the myelin destruction that plagues patients with the disorder.

Experimental Treatments Show Promise

One treatment uses alpha interferon, an anti-viral compound produced by the immune system that also hampers production of the DR2 grooves on cell surfaces. In a preliminary study by Kenneth Johnson, M.D., of the University of Maryland in Baltimore, a small number of multiple sclerosis patients given regular injections of alpha interferon had progressively fewer attacks. And since the start of the program four years ago, Johnson has observed no worsening of overall neurologic function or degree of disability in the treated patients. No long-term adverse side effects were noted.

Radiation treatment designed to “knock off” T cells, McFarlin says, has also stabilized—for up to four years so far—disease progression in 18 of 27 patients treated with severe forms of multiple sclerosis. The patients, studied by Stuart Cook, M.D., of the New Jersey Medical School of Newark, were given total lymphoid irradiation intermittently over a five-week period. Radiation was directed to the spleen and to lymph nodes in the neck, armpit, chest, abdomen, and groin—tissues that produce T cells. The patients suffered no serious side effects from the treatment.

Research that clearly demonstrates the safety and effectiveness of these and other experimental therapies involving immune-suppressing drugs is needed, however, before the Food and Drug Administration can approve them for treatment of multiple sclerosis. Often a treatment that seems worthy in preliminary studies doesn't pan out in controlled trials with larger numbers of patients.

In the meantime, several drugs can be used to counter some of the symptoms of multiple sclerosis. Short-term administration of ACTH (adrenocorticotrophic hormone) and steroids such as prednisone can shorten the duration of attacks. These immune suppressants don't impede the long-term progression of the disorder, however, and can cause mood changes, fluid retention with consequent weight gain, high blood pressure, and ulcers. Patients given ACTH often must be hospitalized for continual monitoring for side effects.

Aspirin, acetaminophen, and other painkillers may relieve the occasional pain some multiple sclerosis patients experience. If the pain stems from muscle spasms, an anticonvulsive such as carbamazepine or muscle relaxants such as diazepam and dantrolene sodium may also help. The constant pain that afflicts some people with severe multiple sclerosis is more difficult to relieve. Tricyclic antidepressants such as amitriptyline may be helpful. Drugs that relax the bladder, such as amitriptyline, can help alleviate urinary frequency and urgency in patients with these problems.

Preventive measures are also beneficial. Overexhaustion, emotional stress, viral infections, and a rise in body temperature (from a hot bath or hot and humid weather, for example) are thought to trigger or worsen symptoms and should therefore be avoided. Patients should also follow a well-balanced and nutritionally sound diet and maintain a desirable weight.

Patients with muscle stiffness may be aided by physical therapy, and moderate exercise can help keep limbs supple and maintain muscle function. Certain exercises can also alleviate spasms.

Occupational therapy can provide multiple sclerosis patients with techniques or devices that help them perform their normal daily tasks. For example, “reachers” that help open cabinet doors, devices that aid with opening plastic bags and boxes, and a swiveling wall mirror that enables a person to see into a pan while it is bubbling on the stove can allow a wheelchair-bound patient to continue to cook meals.

Counseling can help alleviate the emotional stresses felt by multiple sclerosis patients and their families. Many people feel depressed, angry and frustrated when first confronted with their diagnosis. Part of the difficulty in coping with the disease—both for patients and families—stems from the unpredictability of the severity and frequency of symptoms. Most local chapters of the National Multiple Sclerosis Society offer counseling referrals and support groups for people affected by the disease. ■

Margie Patlak is a free-lance writer in Portland, Ore.

For More Information

For more information, contact your local chapter of the National Multiple Sclerosis Society. This organization offers a variety of services designed to provide practical assistance, emotional support, and accurate information to multiple sclerosis patients and their families. Information on research advances in multiple sclerosis can also be obtained from the information office at the National Institute of Neurological and Communicative Disorders and Stroke, Building 31, Room 8A06, Bethesda, Md. 20892.

TOP 10 LABORATORY TESTS:

Blood Will Tell

by Dixie Farley

The heart flutters, the palms moisten, and the patient looks away as the nurse draws blood from a vein.

Another medical test. Is it really necessary?

With today's seemingly endless rise in health-care costs, insurance providers and even health professionals are asking that question. Patients, too, should ask questions so they can be as informed as possible about whether a recommended test is safe and needed. That's the judgment of both the Health Industry Manufacturers Association, whose member companies make instruments and equipment used in the tests, and the College of American Pathologists, physicians who are ultimately responsible for interpreting test results. To help with that "informing,"

FDA Consumer is this month beginning a series of articles on the most common in vitro diagnostics, tests on samples of tissue and fluids taken from the body.

* * * * *

The leading *in vitro* diagnostics happen to be blood tests. It's not hard to figure out why.

Always on the move throughout the body, blood takes oxygen, nutrients, and other essentials of life to every cell. It carries away wastes of cell metabolism, transports hormones from the glands to appropriate sites in other tissue, protects against foreign invaders, and helps maintain a safe temperature. Moreover, this giver and sustainer of life is a veritable barometer of health, which is why blood tests can provide abundant clues to the body's well-being. The top 10 tests, known as "chemistries," analyze blood for glucose, creatinine, blood urea nitrogen, lactic dehydrogenase, bilirubin, potassium, chloride, sodium, calcium, and carbon dioxide.

Nowadays, various "chemistries" from a single blood sample can be run simultaneously, thanks to automated instruments such as the sequential multiple analyzer and, in physicians' office laboratories, small table-top analyzers. Sometimes, samples are put on a plastic slide (dipstick) for insertion into a machine that "reads" the samples much like an instant camera takes a picture. Automated machines can be programmed to identify blood specimens, separate plasma from serum, select specified tests, add needed chemicals (which vary with the test), and quickly calculate results. A computer printout shows both the patient's test results and the normal range for each test. Abnormal levels may be flagged. These analyzers and most other laboratory equipment are regulated as medical devices by the Food and Drug Administration's Center for Devices and Radiological Health, whereas laboratories themselves are the province of the Health Care Financing Administration. (See "Watching the Testers," page 23.)

Blood chemistries are performed on plasma (the fluid part of blood) or serum (the watery portion of clotted blood). As a rule, the blood sample—a teaspoon or so—is taken from an arm vein. When this isn't practical or when only a few drops are needed for one or two tests, the sample may be drawn from a finger, ear, big toe, or heel. Some tests require special directions for the patient,

such as fasting, that must be carefully followed so as not to skew results. It's also important to report any medications being taken, as certain drugs can distort the findings.

Depending on the laboratory equipment and the sex and age of the patient, the normal range of a substance in the sample can vary. Thus, the "normals" listed for the following tests are only examples, taken from *Clinical Laboratory Tests*, by Kathleen Treseler, a nurse educator at Seattle University. The way the tiny measurements are expressed differs from test to test. These terms are described in "Terminology of Lab Testing," page 26.

Glucose and the Fuel System

Measurement: The amount of glucose in serum.

Normal range: 60 to 110 milligrams per deciliter (mg/dL).

Use: To determine whether the body is regulating glucose properly. The test is vital for diabetics.

Comments: Several organ systems help make glucose—a type of sugar that is the body's main fuel—available for use. The small intestine, for instance, absorbs different types of sugar taken in from a meal. Glucose enters the bloodstream immediately; other sugars must be converted into glucose by the gut or liver. The liver also converts proteins and other nutrients into glycogen (a carbohydrate) and fat for storage and, when necessary, changes the stored nutrients back into glucose. Glucose regulation is affected by various hormones, but the main influence comes from insulin, a hormone (secreted by the pancreas) that helps glucose enter cells where the body can use it.

The *fasting glucose* test shows roughly how well the body regulates glucose and, if there's a problem, what's likely to be causing it. The patient is told not to eat or drink anything but water for eight hours before the blood sample is to be drawn. Often, a *two-hour, after-meal* test is used. It shows how well the body handles a measured amount of glucose. Usually, "fasting blood" provides a base. The patient is then given a measured amount (about 100 grams) of glucose. Exactly two hours later, a second blood sample is taken to see whether the patient's glucose level has returned to normal.

Significance of results: Abnormal levels may reflect problems with any of the complex body systems needed to process glucose. Usually, diabetes mellitus is at the root of excess blood sugar. But there are other causes, such as tumors of the pancreas, severe stress, thyroid overactivity, and use of diuretics. Low blood sugar levels, on the other hand, seldom indicate illness. Blood sugar normally drops after exercise or after a meal is digested. Low levels are seen in diabetics who overdose with insulin and in infants, because they process food quickly.

Creatinine and Kidney Function

Measurement: The level of creatinine in serum.

Normal range: 0.7 to 1.5 mg/dL.

Use: This and the blood urea nitrogen test (see below) are commonly used together to test kidney function, though the creatinine

(continued on page 24)

Watching the Testers: Regulation of Clinical Labs

With Americans spending about \$30 billion a year on laboratory diagnostic tests, this industry is big business. It's also serious business—so serious, in fact, that the federal government recently enacted legislation to provide stricter controls over laboratories to improve the accuracy and quality of the tests they perform.

The Clinical Laboratories Improvement Amendments were signed into law Oct. 31, 1988, to strengthen laboratory performance requirements under the Public Health Service Act. Regula-

tions to enforce those requirements are managed by the Health Care Financing Administration, in consultation with the Centers for Disease Control and FDA. Previously, federal rules applied solely to clinical laboratories engaging in interstate commerce or applying for Medicare reimbursement. The amendments, however, extend HCFA authority to all laboratories, including the 100,000 to 150,000 located in physicians' offices. Most requirements will go into effect in 1990.

Not only the federal government but

about half the states have passed some type of clinical laboratory legislation.

FDA's Center for Devices and Radiological Health regulates laboratory equipment used to carry out medical diagnostic tests. The Medical Device Amendments of 1976 require that the center pass judgment on all such tests, except those restricted to research and tests performed at licensed blood banks and plasmapheresis centers, which come under the purview of FDA's Center for Biologics Evaluation and Research. ■

*Depending on the model, automated clinical laboratory analyzers such as this can run from 2,600 to 7,800 blood tests per hour.
(Photo courtesy Olympus Corporation, Lake Success, N.Y.)*



Scheduled for a Test? Here Are Some Things to Ask

Some 20 percent to 60 percent of diagnostic procedures are done unnecessarily, at a cost of \$6 billion to \$18 billion a year, according to the Blue Cross and Blue Shield Association. Such tests provide results with no bearing on the medical evaluation. Moreover, they increase the chances for false reports of abnormalities, which beget needless worry and further unnecessary testing that may be more

costly, even risky. To make sure a recommended test is necessary, appropriate and safe, the Health Industry Manufacturers Association and College of American Pathologists suggest patients ask:

- What is the test for?
- What can be learned from the results?
- What would be changed if the test were omitted?

- Is there any risk? If so, how does it compare with the risk of not taking the test?
- Is there an alternative to the test?
- Is a backup or confirmatory test needed?
- What does the manufacturer's label say about the accuracy of the test?
- What are the qualifications of the laboratory performing the test? ■

A prick of the patient's finger is all that's needed to obtain blood for a glucose test.

(Photo by Arthur Hall III)



(continued from page 22)

test, considered more sensitive, is often used alone.

Comments: Creatinine is a waste product of normal protein breakdown in muscle tissue. Ordinarily, the kidneys filter creatinine from the blood at a steady rate and dispose of it in the urine. Testing for the substance in serum indicates whether the rate is normal and the kidneys are working properly.

Significance of results: A high level mainly results from kidney disease. It may, however, merely reflect heavy exercise or a diet high in red meat. Low serum creatinine levels are seen in patients with muscle wasting diseases such as muscular dystrophy.

Blood Urea Nitrogen (BUN) and Kidney Function

Measurement: The level of urea nitrogen in serum.

Normal range: 4 to 22 mg/dL.

Use: To test kidney function (but rarely used alone for this purpose).

Comments: Like creatinine, urea nitrogen is a waste product of protein metabolism. It is produced by the liver and excreted by the kidneys. BUN and creatinine increases provide indicators (along with others) of chronic kidney failure and the need for dialysis.

Significance of results: As with creatinine, BUN is elevated mainly in kidney disease. But high levels also may accompany dehydration, long-term fever, bleeding ulcer, or congestive heart failure that has stemmed blood flow to the kidneys. Lethargy and confusion are frequent signs of increased urea nitrogen. Decreased BUN in the absence of other signs probably is insignificant.

Lactic Dehydrogenase and Heart Attack

Measurement: The amount of lactic dehydrogenase in serum.

Normal range: 60 to 220 international units per liter.

Use: Mainly to monitor patients with diagnosed or suspected heart attack.

Comments: The enzyme lactic dehydrogenase (LDH) plays an important role in making carbohydrates available to the body. LDH is found chiefly in the skeletal muscles, liver, heart, pancreas, spleen, and brain and, at lower concentrations, in lymph nodes, lungs, and thyroid and adrenal glands. When injured, those tissues release LDH into the bloodstream in amounts proportional to the extent of the damage.

Significance of results: LDH blood levels rise 12 to 24 hours after a heart attack and stay high as long as inflammation persists. For this reason, physicians use this test to help determine whether a heart attack has occurred and may, in fact, test patients daily when heart attack is suspected. Increased LDH may also help to assess severity of liver disease. High levels can mean kidney disorders, infectious mononucleosis, or pernicious anemia, but further tests may be needed to specify which tissue is involved. Low LDH has no health significance.

Total Bilirubin and Bile Excretion

Measurement: The level of bilirubin in either serum or plasma.

Normal range: 0.1 to 1.2 mg/dL.

Use: To determine whether the body can rid itself of bile.

Low levels of bilirubin are of little importance, but high levels can indicate infection, pancreatic cancer, and some types of poisoning.

Comments: Bilirubin is an orange-yellow pigment formed when the spleen (an oblong organ near the heart and stomach) destroys old or damaged red blood cells. Normally, bilirubin binds in the spleen with albumin protein and then travels in the blood to the liver for conversion to a form the body can excrete. The new form passes to the intestines to be changed again. Some is then excreted from the body in stool, some moves on to the kidneys for excretion in urine, and some returns to the bloodstream. An obvious sign that the mechanism is askew is jaundice, a yellowing of the skin and whites of the eyes caused when excess bilirubin invades and stains the tissue. All patients with jaundice are tested for bilirubin.

The test requires fasting, except for water, for eight to 12 hours before the blood sample is taken.

Significance of results: Low amounts are of little importance. Small increases in adults who chronically overproduce bilirubin may lead to gallstones (made up mainly of bilirubin) but are otherwise relatively harmless. High levels, though, can stem from infection, pancreatic cancer, certain types of poisoning, sickle cell and other anemias, and blood-filled tumors. Premature infants and underweight, full-term babies commonly have excess bilirubin because the liver is immature; this usually clears up within a few days of birth as liver function improves. Neonatal jaundice may also be traced to red blood cell disorders, incompatibility with the mother's blood type, and exposure in the womb to drugs such as sulfa or vitamin K taken by the mother shortly before delivery. Continued high levels may lead to bilirubin deposits in the brain and spinal cord, a condition called kernicterus, which can lead to brain damage and death.

The following tests are for electrolytes and for carbon dioxide, which usually is tested at the same time. Obtained from the diet, electrolytes are electrically charged compounds that circulate in body fluids to transmit nerve impulses, contract muscles, and control fluid levels and acid-alkaline balance. If the electrical charge is positive, the compound is called a "cation"; if it's negative, the term "anion" is used. (See also "Electrolytes, the Charge in the Body's Power System" in the July-August 1986 *FDA Consumer*.)

Potassium and Acid-Alkaline Balance

Measurement: The concentration of potassium in plasma.

Normal range: 3.5 to 5.5 milliequivalents per liter (mEq/L).

Use: To monitor patients with a history of disease associated with potassium abnormality—for example, people with heart or kidney disease, high blood pressure (especially when diuretics are given), diabetes, or chronic diarrhea.

Comments: As the principal cation in fluid inside cells, potassium has many important functions, including maintaining acid-alkaline balance, activating enzymes, processing and storing carbohydrates, and helping to send nerve impulses to the heart and skeletal muscles. The body cannot store this vital substance, so it's important to eat foods rich in potassium daily. These include apricots, orange juice, bananas, dates, figs, avocados, prunes,

and tomato juice. Seek medical advice, though, before taking potassium supplements.

Significance of results: Too much circulating potassium—*hyperkalemia*—is due most frequently to kidney disease that interferes with potassium excretion. Also, a deficiency in adrenocortical hormone can lead to hyperkalemia. Abnormally high potassium levels can result from a severe burn or crushing injury. In these cases, potassium is released from damaged cells more quickly than the kidneys can eliminate it; the shock that may accompany severe trauma compounds the problem by slowing kidney function. Twenty-four hours after such an injury, the situation is reversed as fluid enters the circulation to bring potassium levels down. Too much potassium can cause diarrhea, irritability, muscle cramps, and ultimately irregular heartbeat and death.

Too little potassium is called *hypokalemia*, which can lead to or result from alkalosis, an abnormal alkaline state. Among other causes of hypokalemia are prolonged intravenous feeding of a potassium-free solution, liver disease associated with alcoholism, and excessive potassium loss from chronic diarrhea or long-term use of diuretics. Severe depletion can lead to death. Symptoms of potassium loss include weak pulse, falling blood pressure, and weakness.

Chloride, a Team Player

Measurement: The amount of chloride in serum.

Normal range: 97 to 108 mEq/L.

Use: Problems develop less often with chloride than other electrolytes. Any that do show up usually are related to abnormal levels of other electrolytes. Hence, this test is used in conjunction with a test for another electrolyte.

Comments: The primary anion in the fluid outside cells, chloride teams with sodium (table salt is sodium chloride) to regulate fluid pressure across cell membranes.

Significance of results: Chloride levels decrease when the body has lost excessive fluid. This causes bicarbonate to increase to maintain the necessary anion level in serum, which, in turn, can lead to alkalosis. Symptoms of alkalosis include nervousness and numbness or tingling in the hands or feet.

Chloride is elevated in kidney inflammation, overactive thyroid, anemia, and heart disease.

Sodium and Fluid Balance

Measurement: The amount of sodium concentration in plasma.

Normal range: 136 to 145 mEq/L.

Use: Candidates for sodium testing include older people who may not drink enough water, people who may be dehydrated, patients taking certain drugs (lithium, for example), and patients who have experienced a rapid change in weight or mental status. People with a chronic illness such as kidney failure, congestive heart failure, or cirrhosis also may need periodic sodium testing. This test is not a measure of total body sodium, so it is not intended to show, by itself, whether a patient should alter sodium intake. Water retention can, in fact, cause a low *plasma* sodium

(Continued on page 27)

Terminology of Lab Testing

Accuracy: How well a test's results match the actual concentration of the measured substance in the specimen tested.

Confirmatory test: A follow-up test after a positive screening test. Confirmatory tests often are more technically demanding and time-consuming than screening tests. They also can be more costly—in terms of both risk and money—which is why screening is done first.

Deciliter: A unit of volume equal to 0.1 liter or 100 milliliters.

False negative: A finding that wrongly indicates normalcy.

False positive: A finding that wrongly indicates an abnormality.

Gram: A unit of weight equal to 0.03527 ounce.

International unit: An amount defined by the International Conference for Unification of Formulae—used to express the quantity of certain substances, including enzymes such as lactic dehydrogenase.

In vitro diagnostic: A test performed on a specimen of body fluid or tissue removed from the body, as opposed to an *in vivo* test, which is performed on the body itself.

Liter: A fluid measure equal to 33.8 fluid ounces.

Milliequivalent: A term used to

express concentration in tests for electrolytes.

Milliliter: One-thousandth of a liter.

Precision: A test's ability to produce the same results when repeated on the same specimen.

Screening test: Method to rapidly identify unrecognized diseases or conditions. These tests sort out apparently well people who probably have the problem from people who probably don't. Positive or suggestive findings are a clue to the doctor to take a closer look with confirmatory testing.

Sensitivity: A test's ability to indicate an abnormality where there is one.

Specificity: A test's ability to indicate normalcy where there is no abnormality. ■

A technician inserts a small tube of blood into a glucose test pack, which will then be placed in a table-top analyzer to determine the patients's blood glucose level. (Photo courtesy Abbott Laboratories, Abbott Park, Ill.)



Measuring calcium levels can provide evidence about bone disease, certain cancers, kidney failure, or overactivity of the parathyroid gland.

(Continued from page 25)

level when the *total* body sodium actually is increased.

Comments: Sodium's major role is to maintain fluid balance. It accounts for 90 percent of the cations in fluid outside of cells. Sodium attracts water; hence, increased sodium concentration draws water out of cells, causing them to shrink and sometimes malfunction. To compensate, the adrenal gland secretes less of the hormone aldosterone, and that causes the kidneys to step up sodium excretion. When sodium concentration is low, the process is reversed: Elevated secretion of aldosterone causes the kidneys to reabsorb sodium, which leads to water retention.

Significance of results: Increased sodium concentration in plasma is seen mostly in the elderly and in very ill patients. It suggests water loss in excess of sodium loss (as in severe vomiting or diarrhea or the excessive urination of diabetes insipidus) or sodium increase in excess of water (as in people who don't drink enough water and are dehydrated). On the other hand, low sodium concentration can occur if sodium loss exceeds water loss during a severe water-loss situation (as in prolonged diarrhea) or if sodium is inadequately conserved (as in chronic kidney disease). Low sodium concentration also can indicate insufficient aldosterone. An abnormally low sodium level generally causes symptoms such as fatigue, weakness, apprehension, and convulsions. Dry, sticky mucous membranes, flushed skin, elevated body temperature, lack of tears, and thirst are among the symptoms of sodium excess.

Calcium, a Possible Clue to Many Problems

Measurement: The level of calcium in serum.

Normal range: 9.0 to 10.5 mg/dL.

Use: To gather evidence about bone disease, certain cancers, kidney failure, or overactivity of the parathyroid gland.

Comments: Calcium is absorbed from the diet and excreted in both urine and stool. Most of the body's calcium is combined with phosphate and carbonate and serves to strengthen the bones. Only about 10 percent is in the form of electrically charged particles circulating in the blood. Nevertheless, calcium cations are essential for nerve impulse transmission, heart activity, and blood clotting. When serum calcium drops below normal, the parathyroid releases a hormone that triggers a series of events: The gastrointestinal tract absorbs more calcium, the kidneys break down and assimilate calcium, and the bones release calcium into the blood. When serum calcium levels return to normal, this hormone secretion decreases.

Significance of results: Too much dietary calcium, too much vitamin D, prolonged immobilization (as in bed rest), leukemia, bone tumors, parathyroid overactivity, kidney disease, some cancers—all can contribute to high blood calcium. Symptoms include constipation, decreased appetite, nausea, weight loss, kidney stones, and deep body pain. Daily exercise such as walking (or isotonic exercises by people confined to bed) can help

maintain normal calcium levels. Calcium deficiency can occur when the small intestine doesn't properly absorb the mineral, as happens with inflammation of the pancreas and Crohn's disease. Some calcium is bound to protein, so too much protein intake causes the bound calcium to leave the bones and be excreted, leading to the bone-thinning disease osteoporosis. Removal of parathyroid tissue (which can happen during a thyroid operation) causes calcium loss. A person in need of calcium may have tingling in the finger tips, muscle cramps, numbness, and overactive reflexes. Foods rich in calcium include milk and other dairy products, broccoli, collards, tofu, and canned sardines or salmon with bones.

Carbon Dioxide and Acid-Alkaline Balance

Measurement: The level of carbon dioxide in serum.

Normal range: 23 to 30 mEq/L.

Use: To help assess acid-alkaline balance.

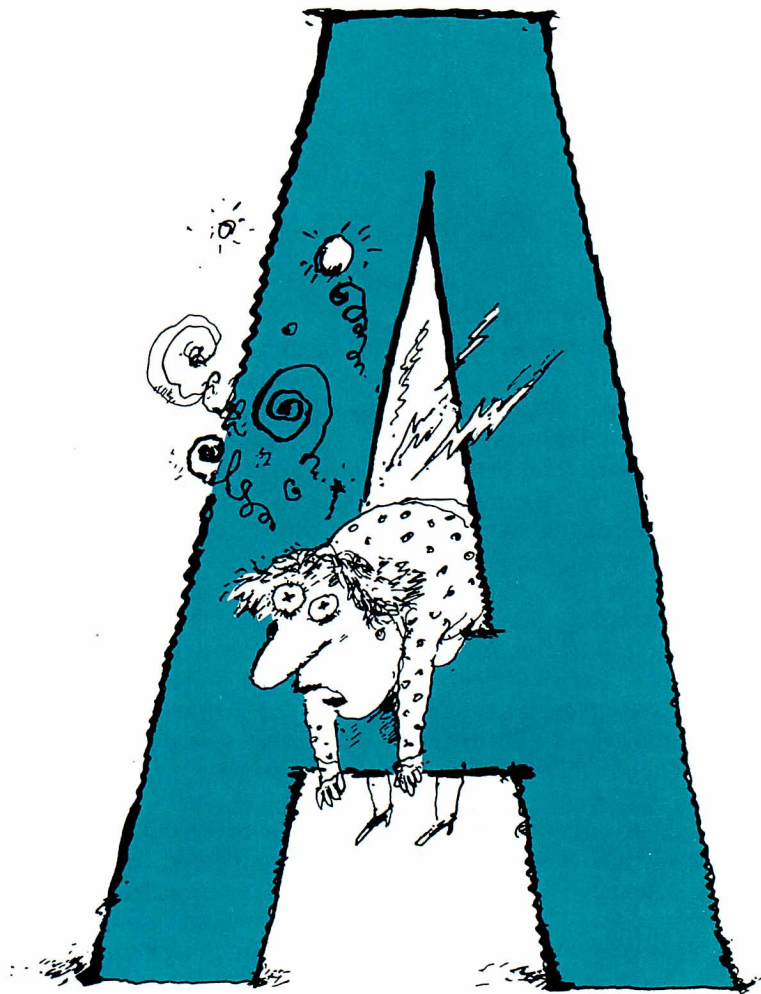
Comments: Carbon dioxide is a colorless gas. Small amounts taken in from the air stimulate breathing, but amounts greater than about 5 percent cause confusion and other abnormal mental activity. Carbon dioxide is the final breakdown product of carbon compounds in food and is eliminated through the lungs, urine and perspiration.

Significance of results: A carbon dioxide increase in blood is seen in alkalosis, which can result from vomiting, overproduction of adrenocorticotrophic hormone, treatment with diuretic drugs, or intake of too much bicarbonate. Carbon dioxide is decreased in the blood in the abnormal acid state, acidosis, and may result from kidney or liver disorders, severe dehydration, or poisoning by substances such as methyl alcohol. Respiratory alkalosis, caused by excessive elimination of carbon dioxide by the lungs, is seen with overdose of aspirin and aspirin-like drugs, an abnormal particle such as a blood clot or air bubble in the lung, or hyperventilation (overbreathing) associated with anxiety, fever or exercise. Respiratory acidosis, caused by excessive retention of carbon dioxide by the lungs, may result from lung disease, oversedation, head injury, congestive heart failure, or burns of the respiratory tract.

Blood chemistry profiles generally aren't considered appropriate for apparently healthy people—in other words, as screening tests. However, recent guidelines developed by the Blue Cross and Blue Shield Association and endorsed by the American College of Physicians recommend individual screening tests for three chemicals: glucose, creatinine and cholesterol. ■

Dixie Farley is a member of FDA's public affairs staff.

In September: The complete blood count.



WHAT CAN BE DONE WHEN THE PAIN WON'T GO AWAY

by Egon Weck

“OUCH!”

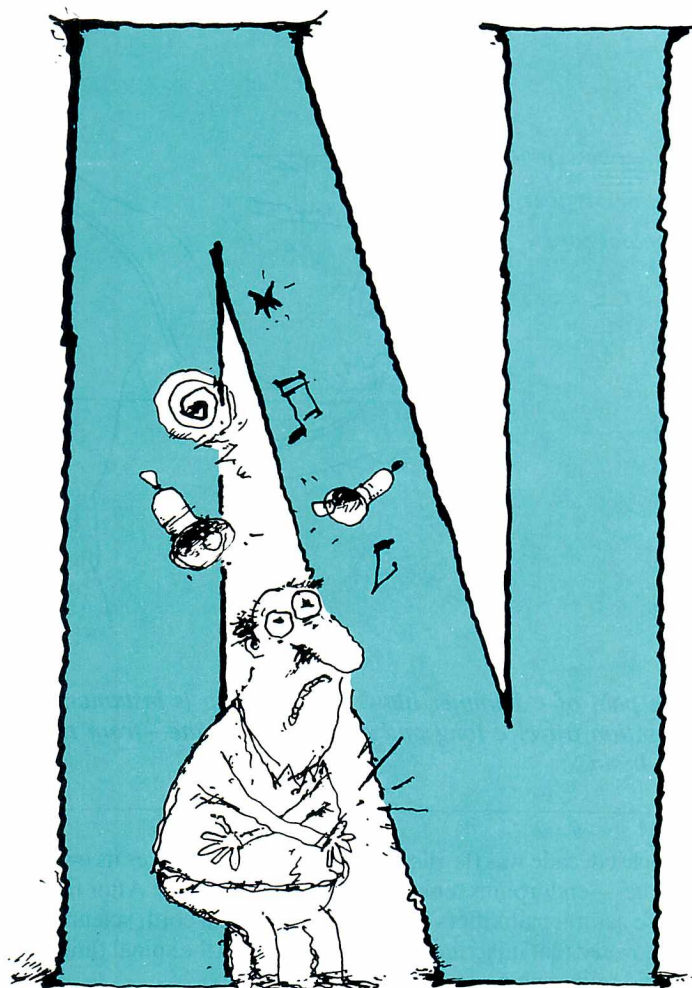
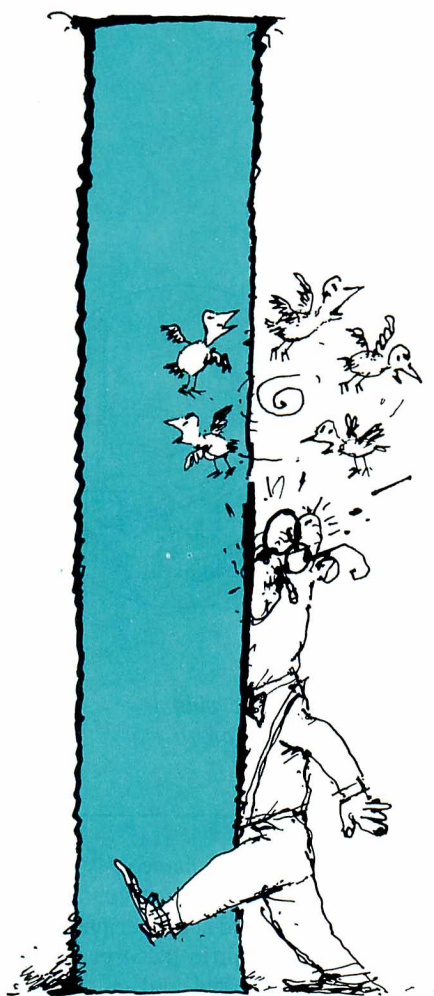
Smash a finger while hammering and your body responds with a jolt of pain that overpowers your other senses and commands: “Stop, you’ve injured your finger!”

Reacting to the sudden pang and the soreness that follows the blow, you immobilize and favor the hurt finger and thereby promote healing.

For the fact is, pain plays a vital biological function. Its importance is dramatically illustrated by people who are unable to feel pain because of disease or injury. Lacking this important warning system, they suffer cuts, burns, broken bones, and other injuries that a sense of pain helps most of us either avoid or react to quickly, preventing worse injury.

But not all pain is useful. Chronic pain that persists long after its cause has been diagnosed serves only to torment the patient. Produced by conditions like a nerve or back injury or cancer, chronic pain has been compared to a burglar alarm that can’t be switched off.

The more research scientists learn about the nature and physiology of pain, the more complex it seems to be. Only recently have medical scientists begun to understand the mechanism of pain. Armed with greater knowledge, they hope to mobilize new resources to control pain.



Moreover, interdisciplinary medical teams focusing on pain at hospitals and pain treatment centers are developing new strategies to treat pain more effectively with traditional painkilling medicines and techniques.

Blocking the Pain Pathway

Pain impulses are sent from the site of the damage to the spinal cord and then on to the brain. The pain from that misdirected hammer blow, for example, is flashed to the nervous system from nociceptors, pain receptors in peripheral tissues—in this case, your thumb. Damaged cells release substances that raise the sensitivity of nociceptors, causing them to send out strong pain pulses.

Prostaglandins are a group of sensitizing substances produced by injured cells. Aspirin and aspirin-like compounds kill pain by inhibiting prostaglandin production by cells of the peripheral nervous system.

Pain can be stopped further up the line—in the spinal cord. Pain impulses originating in peripheral nerves—in your smashed thumb, for instance—travel along special nerve fibers to cells in a part of the spinal cord known as the dorsal horn. In the microscopic spaces—called synapses—between dorsal horn cells, chemical neurotransmitters enable pain messages to move from one cell to

the next on their way to the brain. The dorsal horn cells, however, release a neurotransmitter called serotonin that blocks the passage of pain impulses between cells. Antidepressant drugs such as amitriptyline are thought to prevent nerve cells from pulling serotonin out of the synapses between dorsal horn cells, which may explain why these drugs can relieve pain.

Clinicians are now trying amitriptyline and newer tricyclic antidepressant drugs such as desipramine in patients suffering pain caused by shingles and to treat the severe burning foot pain sometimes associated with diabetes.

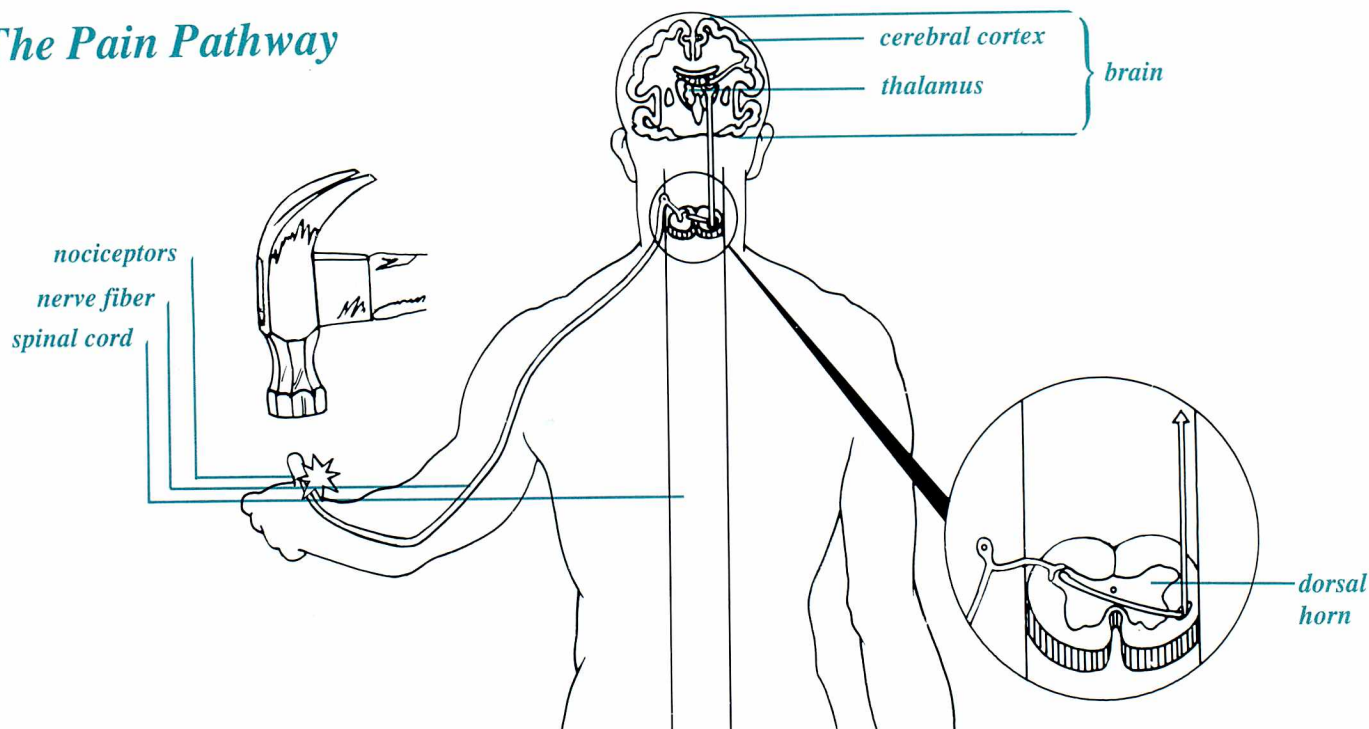
Moreover, they are looking for the substances involved in pain transmission from the peripheral nerve cells to the dorsal horn so they can suppress pain even earlier along this route.

Pain impulses ascend from the spinal cord to the thalamus in the midbrain and then to the cerebral cortex. Morphine, codeine, and other drugs derived from the opium poppy have long been used to control severe pain by causing the brain to suppress pain messages received from the dorsal horn. Synthetic opiates include methadone, hydromorphone and meperidine.

While both natural and synthetic opiate drugs are very effective in handling severe pain, they can have bothersome side effects, including nausea, drowsiness, constipation, and mood changes.

One of the most important breakthroughs in pain research in

The Pain Pathway



The pain of a hammer blow to the thumb is instantaneous. But the impulses transmitting the pain sensation travel a long and complicated route—from the injured area to the spinal cord and on to the brain.

the past decade was the discovery that the body makes its own opiates—endorphins, enkephalins and dynorphins. After finding these natural painkillers in the brain and spinal cord, scientists discovered that injecting opiates directly into the spinal fluid would relieve pain.

They found that very small dosages of opiates injected at sites in the spinal cord where pain is inhibited not only relieved pain, but also prevented some of the side effects associated with large dosages.

Research scientists are also investigating newer opiate-like drugs that they hope will have less troublesome side effects than those caused by currently available drugs.

The Problem of Drug Tolerance

Patients with chronic pain who take opiates for extended periods tend to build up a tolerance to the drugs and need ever larger doses to control their pain. But new findings point to an approach that may enable doctors to circumvent the problem of tolerance.

Researchers have learned that morphine and enkephalins attach themselves to different places on the surface of nerve cells that transmit pain impulses. They speculate that, if enkephalin-like drugs could be developed, patients tolerant to morphine might get effective pain relief by being switched to drugs that mimic the enkephalins.

Pain experts say that many doctors are overly concerned about the risks of opiate dependence in their patients treated for severe pain, such as that caused by cancer. The specialists say these concerns are largely unfounded, basing their assurance on a study of 11,000 hospitalized patients who had been given opiates. Only four patients had any difficulty giving up painkilling medication once it was no longer needed.

Pain experts are now recommending that severe acute pain, like that following major surgery, or the severe chronic pain of cancer

be treated more aggressively by simultaneously administering two or more drugs that act at different pain control sites. To dampen the pain signals generated at the peripheral nervous system, doctors can prescribe aspirin-like drugs. To suppress the pain messages going to the spinal cord and brain, they can use opiates.

The experts say that pain medication works better if adequate doses are begun early and maintained on a regular schedule, before the pain becomes severe. Furthermore, since patients vary greatly in their need for pain relief, they also advise adjusting the dose according to individual need.

Doctors can stop pain cold by blocking the pain at the peripheral nerve level with local anesthetics. Unfortunately, these nerve blocks also shut down other sensations, such as hot and cold, as well as the nerve impulses that control muscles. Another disadvantage: The effects of the anesthetics wear off, and the pain blockage is only temporary.

Pain Control Without Drugs

Severe intractable pain that cannot be successfully controlled by drugs may be relieved surgically by cutting the bundles of nerve fibers in the spinal cord that carry the pain messages from damaged nerve tissues. Called a "cordotomy," the operation blocks pain on the entire side of the body fed by the nerve fibers. But in time the pain tends to return. Other surgical attempts to control pain by severing nerve pathways or destroying nerve tissue also fail to bring enduring relief in many if not all cases. Somehow the body succeeds in establishing other nerve pathways to circumvent the surgically disrupted channel.

Another intriguing approach to pain relief involves the use of electricity. The idea that electrical stimulation can be used to treat pain is hardly new. Some scholars trace it back to ancient Egypt, and we know from historic records that it was used by the Romans.

Safe Use of Analgesics

Most people can safely self-medicate with nonprescription analgesics (pain relievers) as long as they stay within the dosage limits given on the label. Overdosing with aspirin or similar drugs may cause symptoms such as gastric irritation or ringing in the ears. Reye syndrome, a rare but life-threatening malady affecting children and young adults, has focused attention on the safe use of over-the-counter (OTC) pain relievers that contain aspirin. Overdoses of acetaminophen can also be toxic. Extended self-medication with analgesic drugs at recommended dosages may not cause symptoms. But prolonged use without medical supervision may mask a serious illness.

To use OTC analgesics safely:

- Always read the label and follow instructions, cautions and warnings.
- Do not exceed the maximum dosages on the product's label.
- Adults should not take pain relievers for more than 10 days unless directed by a doctor. (For fever, the limit is three days.)
- Children and teenagers should limit use to five days for pain and three days for fever.
- Because of the danger of Reye syndrome (a rare but

sometimes fatal illness), children and young adults (2 to 20 years of age) should not take aspirin for chicken pox, flu, or flu-like symptoms. When in doubt, consult a doctor.

- Those allergic to aspirin should not take any medicine containing aspirin-like ingredients, such as carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate.
- Pregnant women should not take aspirin in the last three months of pregnancy unless instructed by a doctor. Aspirin taken near time of delivery can cause bleeding in both mother and child. ■

Diabetes Patients Sought for Study

Investigators at the National Institutes of Health are seeking diabetes patients suffering from intense, chronic burning caused by nerve damage. They are needed for a clinical trial of the antidepressant drug desipramine, which so far has produced fewer side effects than other antidepressants. Interested candidates should write to Mitchell B. Max, clinical coordinator, Pain Research Clinic, National Institutes of Health, Building 10, Room 3C-405, Bethesda, Md. 20892.

The ancients had to rely on electric eels and torpedo fish as sources of electricity. But in the 19th century, when man-made electricity became first available and then commonplace, electrotherapy was viewed as a panacea. The fact that it turned out not to be gave it a bad name.

In the 1960s, however, two investigators, Ronald Melzack and Patrick D. Wall, proposed a new "gate-control" theory, which provides a scientific rationale for electrical stimulation in the control of pain. They postulated a neural "gate" in the dorsal horn of the spinal cord shared by the large nerve fibers, which carry sensory and motor control signals, and the small ones, which transmit pain impulses. By stimulating large nerve fibers with weak currents of electricity, the gate is closed and pain transmission along the small fibers is shut down, according to the theory.

The work of Melzack and Wall revived the interest of respected research scientists in electrical stimulation therapy. In an experiment at the University of California at San Francisco, neuroscientists are studying the safety and effectiveness of a device that is intended to control pain by direct electrical stimulation of the thalamus. A small battery-powered device worn at the patient's waist sends a radio frequency signal to a receiver implanted just under the skin of the abdomen. Wires under the skin lead from the receiver to one or more pairs of electrodes implanted in the thalamus. By varying the amplitude (strength) of the radio signal, doctors—and, with experience, patients themselves—may be able to control intractable pain that does not yield to other measures. Researchers now believe that the electrical stimulation relieves pain because it causes the brainstem and the spinal cord to release endorphins.

While clinical investigators are reporting some success with the use of electrical implants, this technique is yet to be validated by comprehensive clinical studies. In addition, as with most other

methods of pain relief, the effects of electrical stimulation appear to weaken over time.

Investigators hope that as equipment and techniques improve and as physicians learn to identify the patients who are most likely to benefit, electrical stimulation will prove to be a useful tool for pain management.

TENS, or transcutaneous electrical nerve stimulation, is a noninvasive form of electrical pain control. Electrodes are placed directly on the skin over the painful area or at selected points along the pain nerve pathway. A small battery-powered generator about the size of a pack of playing cards sends pulses of current to the electrodes.

Early experience with TENS convinced some investigators and their patients that it was a promising technique of pain control. However, according to a summary of clinical literature published by the Department of Health and Human Services, after 20 years of experience with TENS, its effectiveness remains uncertain. The department's survey revealed broad variability in pain relief from patient to patient and from one type of pain to another.

Fortunately, to treat the average headache or other minor, short-term ache or pain, most people don't need to seek out a doctor. Instead, they take aspirin, acetaminophen, or some other over-the-counter analgesic until the pain goes away.

But persistent pain often signals an underlying health problem. Headaches can sometimes be a symptom of disorders of the brain, heart and circulatory system, the ear, and the eye. Severe, intermittent headaches may be caused by a brain tumor.

So besides simply looking for relief from pain, when pain persists or recurs, it's good common sense to see a doctor to diagnose and treat its cause. ■

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



The Notebook

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

■ New data are available on the safety and effectiveness of **injectable ivermectin** gastrointestinal drugs for goats. Write Document Control Section (HFV-16), Center for Veterinary Medicine, FDA, 5600 Fishers Lane, Rockville, Md. 20857 (FR March 24).

■ FDA has published tentative final rules for safety and effectiveness requirements for nonprescription drugs to treat **head, pubic and body lice** (FR April 3).

■ FDA has issued a notice of proposed rule-making covering nonprescription **astringent drugs** (FR April 3).

■ **Automated differential cell counters**, used to identify and classify blood elements, have been reclassified from Class III (requiring pre-market approval) to Class II medical devices. Class II devices must meet established performance standards (FR April 5).

■ FDA no longer requires pre-market notification for eight generic types of **surgical devices**, including certain splints and tourniquets, a plastic surgery kit, surgical camera accessories, and an operating table, chair and accessories (FR April 5).

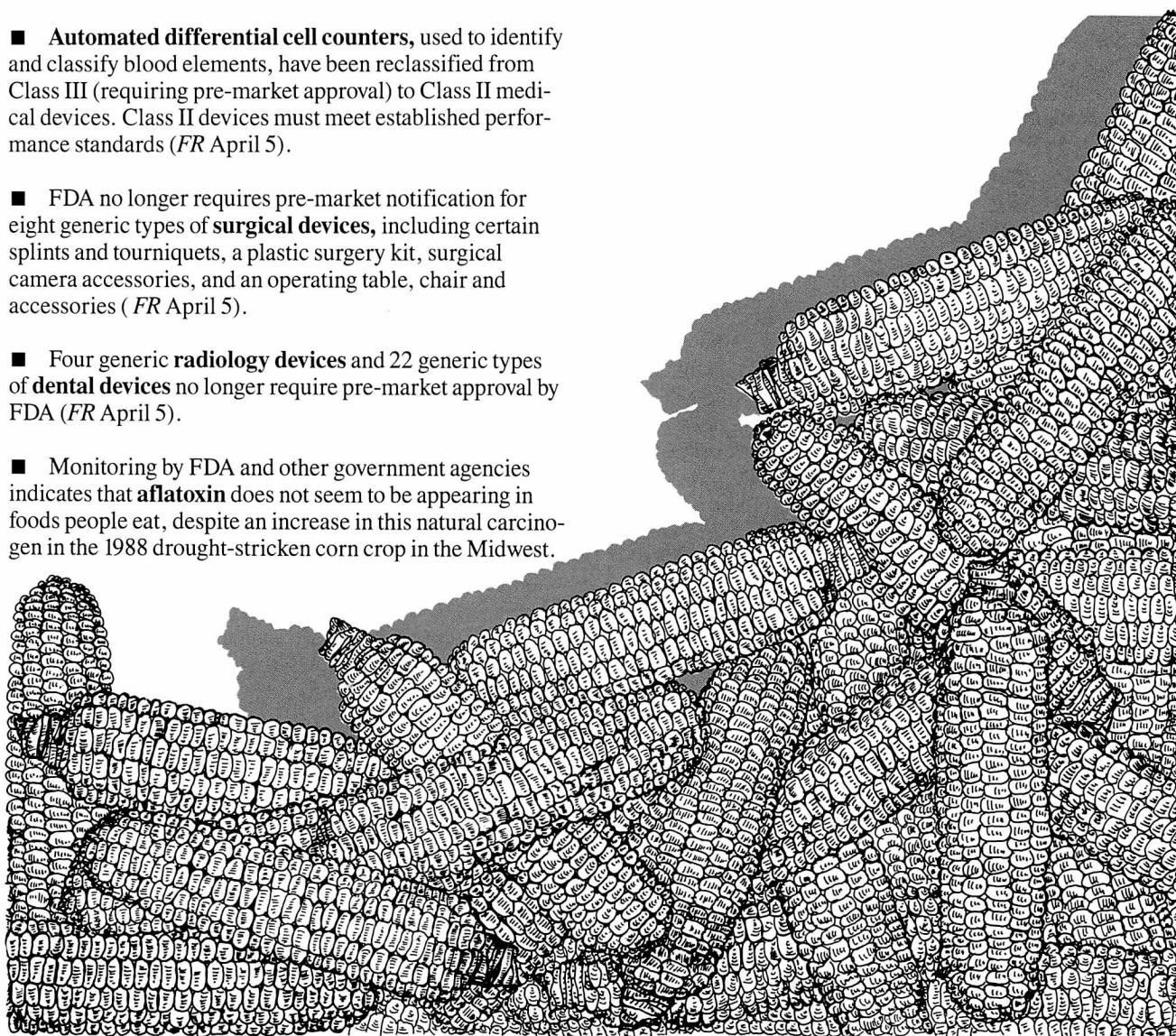
■ Four generic **radiology devices** and 22 generic types of **dental devices** no longer require pre-market approval by FDA (FR April 5).

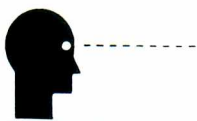
■ Monitoring by FDA and other government agencies indicates that **aflatoxin** does not seem to be appearing in foods people eat, despite an increase in this natural carcinogen in the 1988 drought-stricken corn crop in the Midwest.

■ A change in delegation of authority within the Center for Devices and Radiological Health in FDA is expected to speed response to public **petitions on medical device matters**. The change—consistent with other centers—eliminates the requirement that responses to the petitions be reviewed and approved by FDA's Office of Regulatory Affairs or General Council (FR April 13).

■ FDA has revised its regulations for **good laboratory practices** to further discourage the practice of clipping the toes of certain animals used in nonclinical laboratory studies (FR April 20).

■ FDA has published a new quarterly update of designated **orphan drugs and biological products**. Copies are available from the Dockets Management Branch, FDA, 5600 Fishers Lane, Rockville, Md. 20857 (FR April 21).





Three Jailed for Selling Drug That Killed 38 Babies

by Catherine Carey

Mr. and Mrs. Harris have mixed emotions. Mrs. Harris just gave birth to a boy, three months prematurely. And, while the couple is overjoyed at having a baby, they are sick with worry about the child's health.

To make matters worse, the oxygen being used to keep the baby's underdeveloped lungs working may also be causing an eye disease called retrolental fibroplasia, which could leave him blind.

But the doctors say they have a new drug—a vitamin E solution—that may prevent the blindness while providing an essential vitamin as well. Maybe it will be the answer to their prayers.

But that was not to be. What started out

as a ray of hope for the Harrises ended up tragically with the death of their baby.

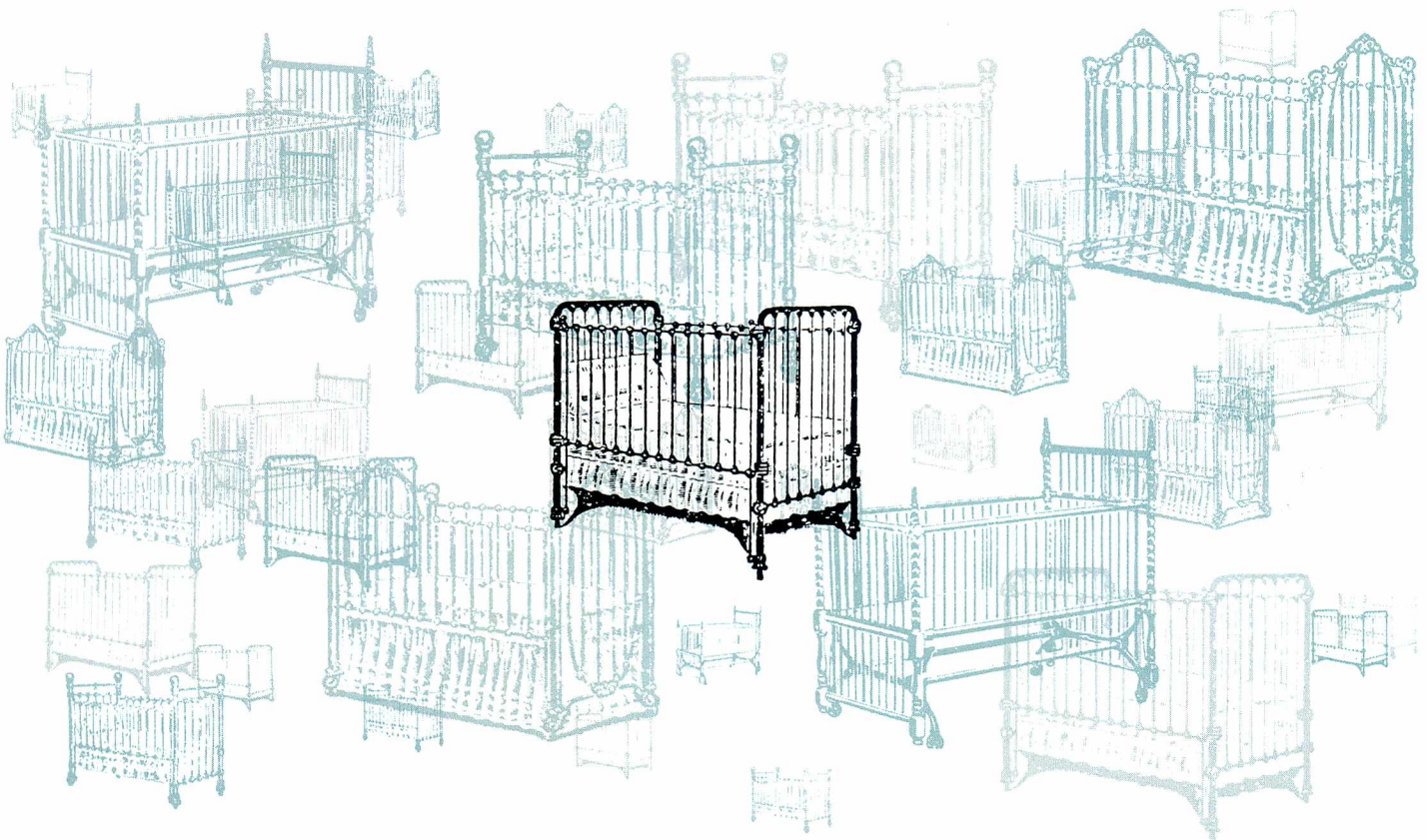
The Harrises are a fictitious couple, but the general scenario was real for parents of 38 premature infants who died after being treated with the vitamin E solution called E-Ferol. Now, those responsible are serving prison sentences after being found guilty of breaking the laws designed to protect the public from such unsafe drugs.

E-Ferol Aqueous Solution was the brainchild of James B. Madison, executive vice president of operations at O'Neal, Jones and Feldman (OJF), a drug distribution firm in St. Louis. Madison, with the permission of his boss, Larry K. Hiland, president of OJF, asked Ronald Carter of

Carter-Glogau Laboratories, a drug manufacturer in Glendale, Ariz., to develop the formula.

Research of the product by Carter-Glogau amounted to no more than determining how vitamin E could be dissolved in water. Neither company submitted a new drug approval application to FDA, explaining later that they believed their product was a nutritional supplement, not a drug. But because the product was labeled for treating a disease—retrolental fibroplasia—the solution was legally a drug.

OJF began distributing E-Ferol Nov. 8, 1983. One month later, the company received the first report of adverse reactions. A pharmacist and a physician at



Kapiolani Children's Medical Center in Honolulu phoned Madison at OJF to report excessive weight gain, swollen abdomens, low blood count, blood clotting abnormalities, and other problems in two infants given the drug. OJF responded by sending them literature on vitamin E.

The second report of adverse reactions came from Sacred Heart Medical Center in Spokane, Wash., on Jan. 24, 1984. A pharmacist from the center called Madison to see if any adverse effects had been seen with E-Ferol. He was told that nothing had been reported. The pharmacist said that the hospital had been using the dosage of E-Ferol recommended in the package insert and several patients had developed unusual symptoms involving kidney function and elevated liver enzymes.

Two days later, on Jan. 26, a specialist in newborns from Sacred Heart called Madison to report that three babies given E-Ferol had died and one was very ill. The physician said that the surviving infant had high levels of vitamin E in its blood. He questioned the safety of polysorbates—ingredients in the E-Ferol preparation—and suggested, in light of the deaths, that the company stop distributing the product, which it did, for a time at least.

On Feb. 1, a pharmacist from the University of Tennessee Hospital in Knoxville called Madison with concerns about the drug. Madison asked if they were having any problems with E-Ferol, and the pharmacist in turn asked if they should be looking for something. Madison told her that nothing in particular had been reported.

Two days later, the pharmacist at Sacred Heart called Madison for more information on E-Ferol, explaining that the drug was the only common factor in the three infant deaths and the sick baby. Madison then suggested, for the first time, that Sacred Heart had used too high a dose of the product, even though it was the dosage recommended in the labeling.

OJF resumed distributing E-Ferol on Feb. 6, 1984. This was just 11 days after the report of the deaths.

On March 26, the University of Tennessee pharmacist called to report that four

babies given E-Ferol had died, presumably from liver failure. Madison still insisted that E-Ferol was safe and promised to send the pharmacist information on the polysorbates used in the drug.

Even though at this point OJF knew of eight deaths (the fourth baby at Sacred Heart had also died) possibly caused by E-Ferol, it continued to distribute the drug until April 6, 1984, when an FDA investigator who inspected the firm that day asked the company to stop.

FDA had become involved in the case in April 1984 when the federal Centers for Disease Control notified the agency of reports it had received from two hospitals of clusters of unusual abnormalities in premature infants in neonatal intensive care units.

The agency had known of the product's existence since November 1983, when health professionals questioned whether it was an approved drug. But lacking information regarding the hazards of this unapproved new drug, the agency had not then taken action to remove it from the market.

Once FDA was alerted to the possibility of adverse reactions associated with the drug, however, it began an investigation immediately.

During the April 6 inspection of the firm, the investigator learned that OJF had known of infant deaths since January. The firm agreed to recall all its E-Ferol and, over the next several days, telephoned all of its accounts. FDA issued a press release concerning E-Ferol and sent recall letters to about 6,600 hospitals and notification letters to about 25,000 pediatricians.

By April 23, 1984, FDA had completed recall audits of all the wholesale distributors and the 159 hospitals that had received E-Ferol, ensuring that all of the product was off the market, as it remains today. But by that time, the infant death toll attributable to E-Ferol had reached 38.

And the story didn't end there.

On July 9, 1987, a federal grand jury in St. Louis indicted the firms of O'Neal, Jones and Feldman and Carter-Glogau, along with Madison, Hiland and Carter, for continuing to market E-Ferol without

FDA approval.

On Sept. 30, 1988, after a seven-week trial, a jury returned guilty verdicts against Carter-Glogau, Ronald M. Carter, Sr., and Larry K. Hiland for distributing an unapproved and misbranded drug with the intent to defraud and mislead, and for participating in a conspiracy to market the drug without testing and without FDA approval. Hiland, the former president of OJF, was also found guilty of mail fraud in connection with the promotion of E-Ferol. He is now serving a six-month suspended sentence in a federal prison. He was also given the option of paying a \$130,000 fine or contributing \$65,000 to research on childhood diseases. Carter received the same sentence as Hiland, and his company, which has since been sold, was fined \$130,000 and ordered to pay an additional \$100,000 in court costs. Both Carter and Hiland are appealing the conviction.

Before the trial, Madison pleaded guilty—thereby giving up his right to appeal—to two counts of wire fraud and one count of misbranding. He is currently serving a six-month suspended sentence in a work-release program that allows him to work for a food bank during the day and report back to prison each evening and on weekends. He was fined \$12,000 but, like Carter and Hiland, has the option instead of paying \$10,000 towards research on childhood diseases.

OJF had also offered a guilty plea before the trial, which the court accepted. The firm was fined \$115,000 and ordered to pay an additional \$125,000 in court costs.

As a result of the E-Ferol tragedy, FDA has changed its policies regarding adverse reaction reporting and its review of drugs similar to those marketed before 1962. (For more information about the new regulations, see "Action on Unapproved Drugs" in the Updates section of the December 1984–January 1985 *FDA Consumer* and "Drug Reaction Reporting" in the June 1985 issue.)

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

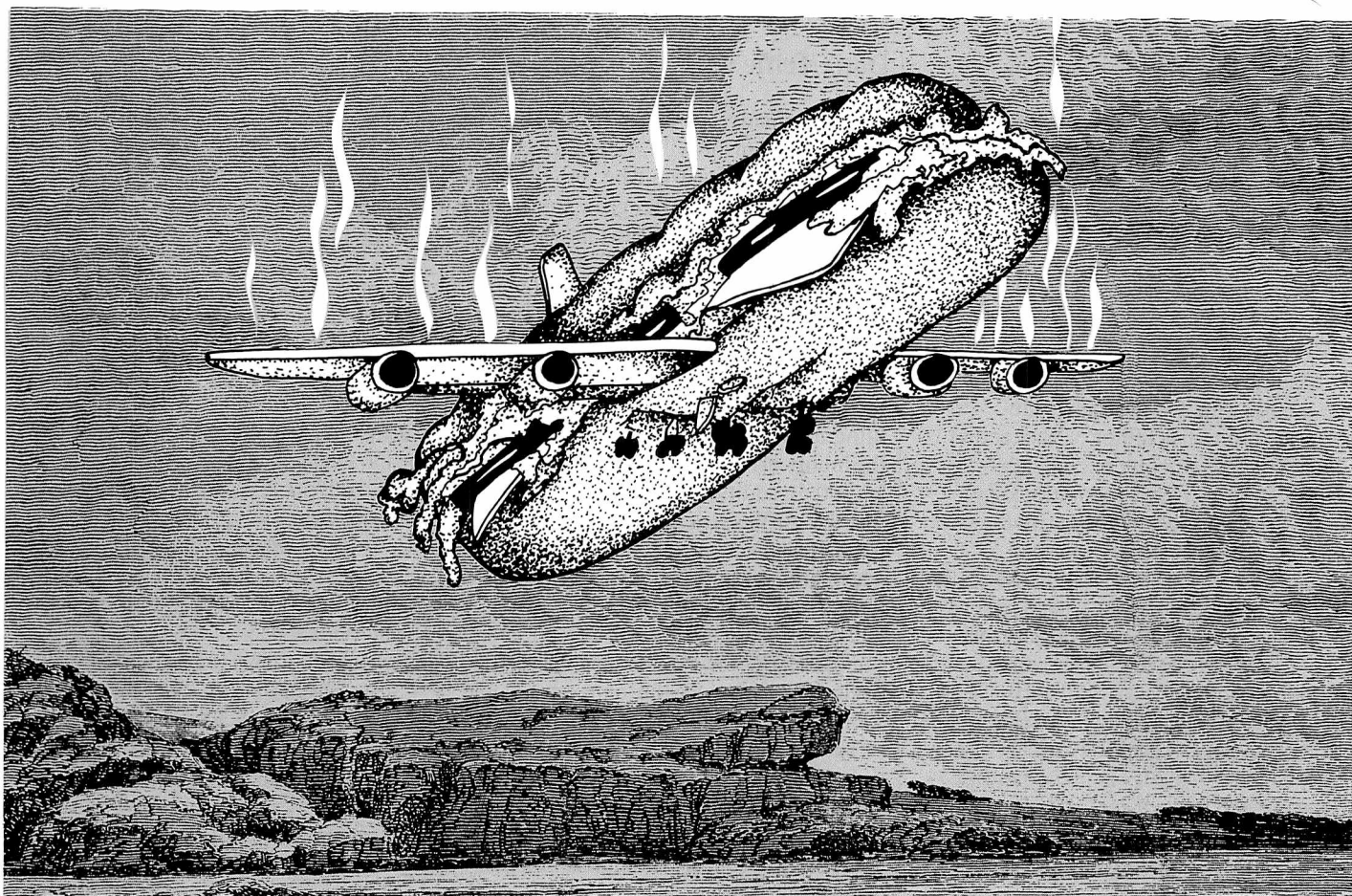
Foul Flying Subs

Tainted submarine sandwiches took the fun out of flying for many travelers on Northwest Airlines flights late last year.

The trouble first came to light when 21 members of the Minnesota Vikings football team suffered cramps, fever, chills, and diarrhea after taking a Northwest Airlines flight from Minneapolis to Miami for their

October 2nd game with the Dolphins. (The Dolphins won by a score of 24 to 7.)

Over the next six weeks, scores of other Northwest passengers suffered the same symptoms, setting off an intensive investi-



gation by local, state and federal agencies, including FDA, which is responsible for sanitation on interstate public transportation. (See "Airline Food Safety Raises Concerns" in the February 1985 issue of *FDA Consumer*.)

Investigators tracked down over a thousand passengers from 253 Northwest flights that traveled through Minneapolis to four countries, 28 states, and the District of Columbia. Seven-hundred-twenty-five passengers were interviewed to determine if those who had eaten food served on the planes had become ill after their flights. Researchers also contacted another 589 Northwest passengers who had not reported becoming ill to establish a control group for their study. Interviews showed a pattern to the illness that indicated the potential for at least 1,000 to 2,500 cases of food poisoning and contamination of as many as 43,100 meals.

Tests of victims' stool samples showed the culprit was *Shigella sonnei*, a bacterium that causes shigellosis. In most cases, symptoms last only a few days, followed by spontaneous recovery.

Investigation into the food poisoning

outbreak traced the source of contamination to the Marriott Corporation's in-flight kitchen at the Minneapolis-St. Paul International Airport. Investigators from FDA and the Edina, Minn., Hennepin County, and Minnesota health departments inspected the kitchen's food handling and storage facilities, interviewed food handlers, and took samples of raw and prepared food for laboratory analysis. Employee health records were screened to see if any had been ill during the outbreak, and all production employees who worked in food preparation during the outbreak were given physical examinations and blood tests.

No major sanitation problems were found. It was concluded that cold in-flight sandwiches had been contaminated during processing by food handlers infected with *Shigella*. The conclusion was based on the following findings:

- No single raw food item was common to all meals associated with the food poisonings.
- All the snacks implicated in the illnesses required hand preparation.
- The comparatively low incidence of ill-

nesses suggested that not all meals were contaminated.

- Two of five food handlers working shifts during which the implicated food was prepared had elevated antibodies, suggesting recent infection.
- Blood samples from all those who became ill during the outbreak contained antibodies unique to the group.

Investigators concluded that probably one or more of the food handlers had picked up the *Shigella* infection in the community and passed it on by contaminating submarine sandwiches while preparing them.

Color It Illegal

The fact that the eye makeup imported from Taiwan was improperly labeled was enough to warrant FDA action. But it also contained unapproved dyes, at least one of which is known to cause serious eye injury in test animals. As far as is known, no one was injured by using these cosmetics, thanks to FDA's prompt response to a tip from a source in the cosmetics industry.

In August 1988, FDA investigators

visited two Los Angeles cosmetics distributors—Cameo Trading Company and Rich-On, Inc.—to inspect Taiwanese makeup the firms were shipping for sale in 40 states, Puerto Rico, Guam, Canada, and Great Britain. Laboratory analysis of the products showed they contained FD&C Blue No. 1, D&C Red No. 7, and D&C Red No. 19, none of which has FDA approval for use in products to be applied near the eyes.

In addition, the labeling for some of the cosmetic kits failed to identify the manufacturer, distributor or packer and did not list the quantity of contents—information that FDA regulations say must be on the label of cosmetics for sale in the United States.

In the fall of 1988, the two firms recalled the violative products, but that corrective action was complicated by the fact that some of the products had been distributed as much as a year-and-a-half earlier. Furthermore, inspections by investigators from FDA's Los Angeles district office showed that cosmetics from numerous Taiwanese manufacturers contained illegal dyes. The agency proceeded to issue a blanket detention covering all eye makeup produced in Taiwan.

The detention order prohibited U.S. firms from receiving the products. In a little over a year, personnel from the Los Angeles office examined more than 190 shipments of makeup from Taiwan. Some of the products failed to meet labeling requirements, while others were found to contain illegal dyes.

The U.S. importers had three options: recondition the products to bring them into compliance with FDA regulations; ship the violative products back to Taiwan; or destroy them. They also had the opportunity to have the products tested for the presence of illegal colors by an independent laboratory. Samples and test results would then be sent to FDA for verification.

Importers were able to recondition cosmetics whose only problem was insufficient labeling. Ninety-one of the shipments were relabeled and subsequently released for sale. At least 64 of the shipments, however, contained eye makeup with illegal dyes, and these have been refused entry. The Los Angeles office reports that the inspection is continuing, but that most importers have elected to ship the makeup right back where it came from.

Don't Trifle with Truffles

The distinctive aroma of fresh truffles is an advantage in the wild. Without it, these gourmet delicacies would be very difficult to find since most truffles grow from 3 to 12 inches underground. But that same aroma proved a liability to a French merchant who recently exported some fresh truffles to the United States.

The merchant was concerned that the truffles' pungent aroma would attract thieves. Although he was shipping only 5 kilograms (approximately 11 pounds) of the highly prized fungus, it was worth over \$2,000. In addition, he wanted to ensure that the truffles still smelled like truffles when they reached their final destination. The merchant's packing method, however, which kept the truffles' identity a secret and the aroma intact, probably left them prey to deadly *Clostridium botulinum*, the bacteria that produce the toxin responsible for botulism.

The fresh truffles, packed in clear, airtight plastic bags, were shipped unrefrigerated to the United States via United Parcel Service on Dec. 13, 1988. UPS brought them into the country through its international import hub in Louisville, Ky., and the import notice was duly submitted to FDA's Louisville resident inspection post. That notice alerted an FDA investigator that something was amiss.

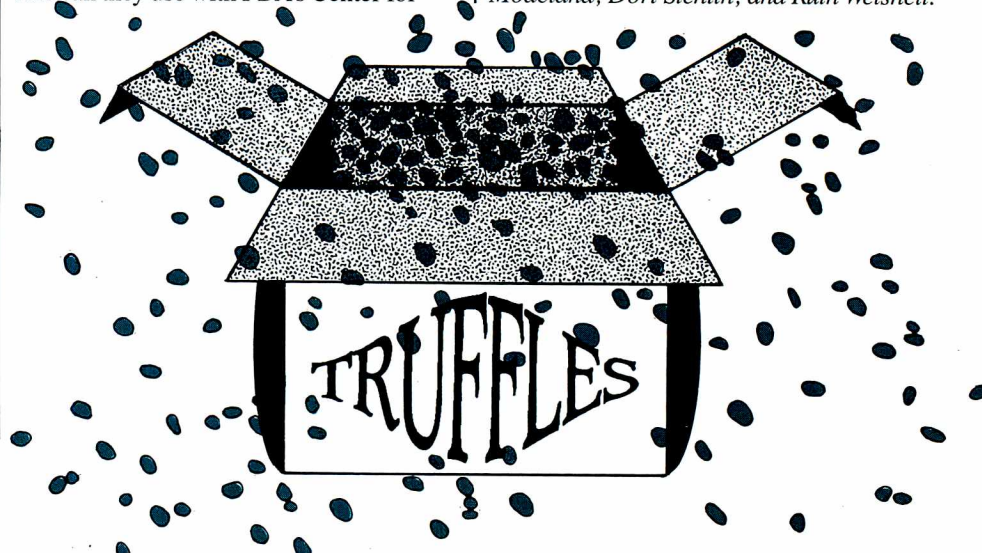
Because all truffles entering the United States via Louisville in the past had been canned, the investigator checked the import notice for required information on the size and number of cans. (Because low-acid canned foods such as truffles can support the growth of *C. botulinum* if improperly processed, canners must file their processing procedure for each product and each size can they use with FDA's Center for

Food Safety and Applied Nutrition, and list the can size on invoices and import notices.) But the notice with these truffles indicated only the weight—5 kilograms.

To determine how the truffles were packaged and whether FDA regulations on listing can size and number had been violated, the investigator went to inspect the shipment on Dec. 14 only to find that the truffles had already been forwarded to a wholesaler in Alexandria, Va. The investigator requested the product be returned to Louisville for inspection, and when the truffles were finally examined on Dec. 20, the packing box was bulging. The investigator cut it open, and styrofoam packing material went flying. The plastic bags were swollen, and dark juice in the bags left little doubt that the truffles had started to decompose. As if that weren't enough, the individual packages bore no labeling—another violation of regulations.

Scientists in FDA's Center for Food Safety and Applied Nutrition determined that fresh truffles packed in airtight plastic bags and shipped unrefrigerated can support the growth of *C. botulinum* bacteria and production of botulism toxin. The agency requested that the truffles be destroyed immediately under Customs Service supervision, but warned that it had to be done carefully to ensure that the plastic bags did not explode and spray the possibly contaminated juice and truffles. FDA also told the merchant and the French embassy in Washington, D.C., that the agency would not allow unrefrigerated fresh truffles packed in airtight bags into the country. The truffles were incinerated on Feb. 1, 1989, without incident.

— This small sample of reports from the field was prepared by Ken Flieger, Vern Modeland, Dori Stehlin, and Ruth Weisheit.





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/Contamination, Spoilage, and Insanitary Handling

PRODUCT: Beans, black, tapioca flour, rice paper, and other food stocks, at San Francisco, N. Dist. Calif.; Civil No. C-88-2240-RFP.

CHARGED 6-6-88: While held by B M Trading Co., San Francisco, Calif., the tapioca flour and the rice paper contained rodent filth—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65484; S. No. 88-378-210; S.J. No. 1)

PRODUCT: Beans, red kidney, dried, at Gonzales, M. Dist. La.; Civil No. 83-0664-B.

CHARGED 6-17-83: While held by Gonzales Products Co., Inc., Gonzales, La., the article had been held under insanitary conditions—402(a)(4).

DISPOSITION: Consent—ordered destroyed. (F.D.C. No. 64041; S. No. 83-383-539; S.J. No. 2)

PRODUCT: Cereal, canned tomato sauce, and other food stocks, at St. Louis, E. Dist. Mo.; Civil No. 88-1946-C-1.

CHARGED 10-6-88: While held by Cherrick Distributing Co., St. Louis, Mo., the tomato sauce was unfit for food due to swollen and leaking containers, and all of the articles had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65551; S. No. 88-526-890 et al.; S.J. No. 3)

PRODUCT: Cocoa beans, at Philadelphia, E. Dist. Pa.; Civil No. 88-6151.

CHARGED 8-10-88: While held by Northern Shipping Co., Philadelphia, Pa., the articles contained bird filth and had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65463; S. No. 88-474-307; S.J. No. 4)

PRODUCT: Coffee beans, at Brooklyn, E. Dist. N.Y.; Civil No. CV-88-1971.

CHARGED 6-22-88: While held by Continental Terminal, Brooklyn, N.Y., the article had been held under insanitary conditions—402(a)(4).

DISPOSITION: Consent—authorized release to J. Aron and Co., New York, N.Y., for salvaging. (F.D.C. No. 65477; S. No. 88-509-256 et al.; S.J. No. 5)

PRODUCT: Conch meat, frozen, at San Juan, Dist. Puerto Rico; Civil No. 88-152 (PG).

CHARGED 1-28-88: While held for sale, the article contained decomposed conch meat—402(a)(3).

DISPOSITION: A motion for leave to intervene was filed by Fish Products Corp., San Juan, Puerto Rico, who asserted that the article had been purchased from Third Wave Development Corp., Miami, Fla., and that the disposition of the action might impair the intervenor's ability to protect its interest. The intervenor also denied the charges and asserted, as affirmative defenses, that the intervenor had not adulterated the article, that the article was not decomposed, and that the intervenor was willing to reexport the article. Subsequently, the government moved to strike the intervenor's answer because the answer lacked a verification upon oath and lacked a statement of the claimant's specific interest in the property. Ultimately, the court struck the answer filed by Fish Products Corp. and entered a default decree of condemnation ordering the article destroyed. (F.D.C. No. 65376; S. No. 88-512-561 et al.; S.J. No. 6)

PRODUCT: Lupini beans, dried, dried navy beans, and other food stocks, at Pittsburgh, W. Dist. Pa.; Civil No. 88-1807.

CHARGED 8-15-88: While held by Starmoolis Brothers Co., Pittsburgh, Pa., the named articles contained rodent filth, and all the articles had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65516; S. No. 88-343-858 et al.; S.J. No. 7)

PRODUCT: Mushrooms, canned, at Twin Oaks (Chester), E. Dist. Pa.; Civil No. 88-4842.

CHARGED 6-20-88: While held for sale, the article was unfit for food due to rusted, detinned and leaking containers—402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65474; S. No. 88-570-446 et al.; S.J. No. 8)

PRODUCT: Peanuts, sugar coated, at Bayamon, Dist. Puerto Rico; Civil No. 88-00883.

CHARGED 5-23-88: While held by Cabrera Distributors, Inc., Bayamon, Puerto Rico, the article contained insects and had been held under insanitary conditions—402(a)(3), 402(a)(4).
DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65464; S. No. 88-512-594; S.J. No. 9)

PRODUCT: **Rice**, at St. Louis, E. Dist. Mo.; Civil No. 88-1001-C-5.

CHARGED 5-20-88: While held for sale, the article contained mammalian filth and had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65461; S. No. 88-526-832; S.J. No. 10)

Dietary Supplement/Vitamins

PRODUCT: **Calcium carbonate tablets**, at Pittsburgh, W. Dist. Pa.; Civil No. 88-1564.

CHARGED 7-18-88: While held for sale, the article, labeled "Advantage . . . Calcium Carbonate . . . Tablets . . . Dist. By: Advantage Supplements, . . . Carnegie, Pa.," had labeling that falsely claimed the article was a dietary supplement of calcium, when the article did not provide bioavailable calcium because the article failed to disintegrate or dissolve in the gastrointestinal tract in time for calcium absorption to occur—403(a)(1); the article's label lacked the street address of the distributor and such address was not listed in the telephone directory—403(e)(1); and the article was represented for special dietary uses but lacked required information—403(j).

DISPOSITION: Consent—ordered destroyed. (F.D.C. No. 65473; S. No. 88-437-569; S.J. No. 11)

Food Additives

PRODUCT: **Cal-O-Tabs calcium orotate-asparate chewable lozenges**, at Buena Park, C. Dist. Calif.; Civil No. 88-05087 DT (GHKx).

CHARGED 8-19-88: While held by Alacer Corp., Buena Park/Burbank, Calif., who manufactured the article using interstate components, the article contained the nonconforming food additive orotic acid—402(a)(2)(C).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65524; S. No. 88-444-390 et al.; S.J. No. 12)

PRODUCT: **Magnesium di-orotate tablets and other products containing salts of orotic acid**, at Farmingdale and Huntington Station, E. Dist. N.Y.; Civil No. CV88-2348.

CHARGED 7-28-88: While held by National Nutritional Laboratories, Inc., Huntington Station, N.Y. and Natural Organics Inc., Farmingdale, N.Y., who were preparing and distributing the products, the article contained the nonconforming food additives salts of orotic acid—402(a)(2)(C).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65479; S. No. 88-520-982 et al.; S.J. No. 13)

PRODUCT: **Magnesium orotate tablets, potassium orotate tablets, calcium orotate tablets, zinc orotate tablets, orotic acid tablets, EPA/GLA capsules, and Co-enzyme Q10 capsules and tablets**, at Fargo, Dist. N.D.; Civil No. A3-88-131.

CHARGED 8-10-88: While held by Swanson Health Products, Inc., Fargo, N.D., the articles (some of which were in bulk and some that were repacked in retail-size containers) were promoted for a variety of unsupported therapeutic and other claims, and the EPA/GLA capsules, the Co-enzyme capsules and tablets, and the tablets containing salts of orotic acid (i.e., magnesium orotate tablets, potassium orotate tablets, calcium orotate tablets, and zinc orotate tablets) were new drugs without effective approved New Drug Applications, and their labeling lacked adequate directions for use for their intended purposes—505(a), 502(f)(1); the orotic acid tablets and the tablets containing salts of orotic acid contained the nonconforming food additives, orotic acid, or salts of orotic acid—402(a)(2)(C); and the EPA/GLA capsules contained the nonconforming food additive gamma linolenic acid—402(a)(2)(C).

DISPOSITION: The articles were initially claimed by the dealer. Subsequently, pursuant to stipulation, the dealer withdrew its claim and a default decree ordered the articles destroyed. (F.D.C. No. 65496; S. No. 88-472-500 et al.; S.J. No. 14)

PRODUCT: **Superoxide dismutase tablets**, at Lynbrook, E. Dist. N.Y.; Civil No. 88-C-2292.

CHARGED 7-22-88: When shipped by Oxford Laboratories, Guttenburg, N.J., the articles, labeled "Solgar Sod (Superoxide Dismutase 2000 units . . .) . . . tablets . . . Solgar Co., Inc., Lynbrook, N.Y.," contained the nonconforming food additive superoxide dismutase—402(a)(2)(C); and the articles' label lacked a list of ingredients by their common and usual names—403(i)(2).

DISPOSITION: Consent—ordered destroyed. (F.D.C. No. 65482; S. No. 88-520-970; S.J. No. 15)

Drugs/Human Use

PRODUCT: **B-A-C barbiturate-analgesic tablets, and Sedapap barbiturate-analgesic capsules**, at Mayrand, Inc., Greensboro, M. Dist. N.C.; Civil No. 88-722-G.

CHARGED 7-14-88: When shipped by Central Pharmaceuticals, Inc., Seymour, Ind., the articles, which bore labels such as "B-A-C-# 3 Tablets . . . Butalbital . . . Aspirin . . . Caffeine . . . Codeine Phosphate . . . Manufactured by Central Pharmaceuticals . . . Seymour, In. . . Mfg. for . . . Mayrand, Inc., Pharmaceuticals, Greensboro, N.C." and "Sedapap #3 Capsules . . . Acetaminophen . . . Butalbital . . . Codeine Phosphate . . . Manufactured By Central Pharmaceuticals . . . Seymour, In., . . . Mayrand, Inc. Pharmaceuticals Greensboro, N.C." were new drugs without effective approved New Drug Applications—505(a).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65483; S. No. 88-538-382 et al.; S.J. No. 16)

PRODUCT: Nystatin, neomycin sulfate, gramicidin & triamcinolone acetonide cream, at Middlesex, Dist. N.J.; Civil No. 86-4042 (HAA).

CHARGED 10-15-86: While held for sale, the article's strength differed from the U.S.P. standard because the article contained 63.2 percent of its labeled gramicidin content—501(b); and the labeling of the article was false and misleading since 0.25 milligrams of gramicidin were declared, but laboratory analyses found less than 0.16 milligrams of gramicidin—502(a).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 64986; S. No. 86-417-957; S.J. No. 17)

PRODUCT: Sore throat spray, at Binghamton, N. Dist. N.Y.; Civil No. 88-CV-157.

CHARGED 2-10-88: While held by Lander Co., Inc., Binghamton, N.Y., who manufactured the article using interstate phenol, the circumstances used for the article's manufacture and processing failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: Consent—ordered destroyed. (F.D.C. No. 65382; S. No. 87-471-274 et al.; S.J. No. 18)

Drugs/Veterinary

PRODUCT: Solu-cillin 50, Solu-cillin 250, and drug component, at Norwood, Dist. N.J.; Civil No. 88-1135.

CHARGED 3-11-88: While held by PBC Enterprises, Norwood, N.J., who was manufacturing or repacking the articles using interstate penicillin G potassium, the articles were new animal drugs, and no approvals of New Animal Drug Applications were in effect with respect to the articles' intended uses—501(a)(5); and the circumstances used for the manufacture, processing, packing and holding of the Solu-cillin 50 and 250 failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65384; S. No. 88-438-392 et al.; S.J. No. 19)

Medical Devices

PRODUCT: Energy Points Stimulator electrical device, at Lawrence, Dist. Kan.; Civil No. 88-4053.

CHARGED 3-18-88: That the article (which had been imported from England, which was labeled "E.P.S. Made in England," and which was accompanied by pamphlets reading "E.P.S. Personal Electro Acupuncture for the Relief of Painful Sporting Injuries" and "The Energy Points Stimulator . . . Acupuncture Without Needles") lacked the required manufacturer's notice of intent to market—502(o).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65395; S. No. 88-473-269; S.J. No. 20)

PRODUCT: Healaid electro-magnetic therapy device for horses, at Santa Barbara, C. Dist. Calif.; Civil No. 87-03467-FFF(Bx).

CHARGED 5-29-87: The articles were accompanied by the distributor's brochure, reading "At Last! Electro-Magnetic Therapy . . . Healaid . . . Distributed by Jack Miller . . . Santa Barbara, Calif.," that contained false and misleading claims for "cuts and bruises" "acute swellings" and "infections" in horses—502(a); and the article's label lacked adequate directions for use, and adequate directions could not be written for such use—502(f)(1).

DISPOSITION: Consent—authorized release to the distributor for bringing into compliance. (F.D.C. No. 65195; S. No. 87-425-212; S.J. No. 21)

INJUNCTION ACTIONS

DEFENDANTS: Pentcal, Inc., and Allyn C. Taylor, chief executive officer, Samuel J. Penta, president, and P. Almond Dell'Orfano, treasurer, Allston, Dist. Mass.; Civil No. 85-1415-T.

CHARGED 4-12-85 in a complaint for injunction: That the defendants, at their plant in Allston, Mass., manufactured, packed, labeled, stored, held, and distributed in interstate commerce various injectable drugs and other drugs; that such drugs were manufactured, processed, packed and held under circumstances that failed to conform with current good manufacturing practice; that some of the defendants' drugs (i.e., iron dextran injection and nitroglycerine injection) were new drugs without effective approved New Drug Applications; that the latter such drugs lacked adequate directions for use and were not exempted as prescription drugs, due to their new drug status; that FDA inspections revealed a number of specified deviations from current good manufacturing practice; and that the defendants were well aware that their activities were in violation of the law—501(a)(2)(B), 505(a), 502(f)(1).

DISPOSITION: Consent decree of permanent injunction enjoined the complained-of violations and enjoined further operations involving interstate components and interstate shipments of drugs, unless and until a number of specified conditions were met, including the following: the establishment of specified current good manufacturing practices, the certification to FDA by an expert that specified requirements had been met, and the destruction or otherwise bringing into compliance of all drugs on hand. (Inj. No. 1107; S. No. 85-302-661 et al.; S.J. No. 22)

MISCELLANEOUS ACTIONS

SUBJECT: Generic version of ceftazidime antibiotic injection and FDA's processing of a ceftazidime monograph, Raleigh, E. Dist. N.C.; Civil No. 85-1503-CIV-5.

CHARGED 11-14-85 by Glaxo, Inc., a drug firm involved in the sale, research and development of new antibiotics at Research Triangle Park, N.C., against HHS Secretary Margaret Heckler and FDA Commissioner Frank E. Young, in a complaint for declaratory judgment and injunctive relief: That the antibiotic ceftazidime had been discovered in 1978 in the laboratories of the plaintiff's parent company and had been patented throughout the world; that because

of earlier licensing arrangements, the plaintiff lacked exclusive patent rights in the United States; that the plaintiff had invested millions of dollars to conduct the research and development activities, including clinical safety and effectiveness studies needed to receive approval in the United States and abroad; that FDA had approved the plaintiff's application for ceftazidime (under the trade name Fortaz) for marketing in the United States; that ceftazidime had been exempt from antibiotic batch certification; that, under Section 507(e) of the FDC Act, approved antibiotics (such as ceftazidime) which were also new drugs and which were exempt from certification were the subject of approved New Drug Applications; that, under the Drug Price Competition and Patent Term Restoration Act of 1984, no applications for approval of a generic version of a new drug approved under Section 505(b) could be submitted until five years after the date of approval of the pioneer drug on which the generic copy was based, unless the generic application contained full reports of adequate clinical investigations; that FDA had announced that the exclusivity provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 did not apply to antibiotic drugs; that Glaxo disputed such announced FDA interpretation and petitioned for a stay by FDA concerning the processing or approval of any generic version of ceftazidime; that FDA denied Glaxo's petition and announced its intention to grant effective approval of applications for generic versions of ceftazidime, even though data to support those applications was not publicly available; that, unless relief was granted to the plaintiff, FDA would imminently approve an application by Eli Lilly Co. for approval of a generic version of ceftazidime that did not contain full reports of adequate investigations conducted by the applicant to establish the clinical safety and effectiveness of the drug, but relied upon the approval of Glaxo's pioneer ceftazidime application based on Glaxo's proprietary safety and effectiveness data; that FDA approval of Lilly's application would deprive Glaxo of its five-year period of exclusive marketing and result in irreparable injury to Glaxo; and that such FDA approval would violate the FDC Act and was unlawful under the Administrative Procedure Act.

The petitioner also alleged as follows: that, based on Glaxo's showing of extraordinary circumstances, FDA had advised that Glaxo's safety and effectiveness data would not be made public but would be treated by FDA as exempt from disclosure as trade secrets; that Glaxo's safety and effectiveness data for ceftazidime had not been made publicly available; that an FDA *Federal Register* statement [in a Notice of Proposed Rulemaking] stated that an applicant seeking to market a duplicate of an approved antibiotic might rely upon the publicly available safety and efficacy data of the pioneer drug; and that FDA's decision to process applications for generic versions of ceftazidime, in the absence of publicly available data on the safety and effectiveness of the drug, violated FDA policy and was therefore unlawful.

DISPOSITION: The government opposed the petitioner's motion for a temporary restraining order and for preliminary injunction. Eli Lilly & Co. moved to intervene and also opposed the petitioner's

motion. The court granted Lilly's motion to intervene. In ruling against the petitioner's motions, the court found to be meritless Glaxo's secondary argument that Lilly's generic ceftazidime might not be approved because FDA agreed not to make public Glaxo's safety and effectiveness data. FDA's agreement could not bar FDA from approving generic ceftazidime; and FDA regulations did not require that approval of generic versions of antibiotic drugs be based upon *public* efficacy and safety data.

As to Glaxo's primary argument, the court noted FDA's traditional approval of antibiotic drugs pursuant to 21 U.S.C. 357 and of non-antibiotic drugs pursuant to 21 U.S.C. 355. The court also noted that, although prior to the 1984 amendments, a generic copy of a non-antibiotic drug would not be approved without such safety and efficacy data as would be required for the initial approval of a non-antibiotic drug, FDA routinely approved generic copies of antibiotic drugs pursuant to 21 U.S.C. 357 without requiring separate safety and efficacy tests for each generic version of an antibiotic drug. For generic antibiotic drugs, FDA created an antibiotic monograph of the approved pioneer antibiotic drug which acted as recipe for an antibiotic drug and its generic copies. The generic copies would receive FDA marketing approval provided the generic copies were identical to the previously approved drug, as described in the antibiotic monograph; and the generic manufacturers were not required to replicate the scientific data accompanying the pioneer antibiotic drug's application.

The 1984 amendment to 21 U.S.C. 505 substantially changed the treatment of proposed generic *non*-antibiotic drugs; and a number of traditional distinctions between antibiotic drugs and non-antibiotic drugs were minimized. In addition, another traditional distinction, batch certification, was to a large extent removed in 1982 by federal regulation. However, the court stated that it could not rewrite the law so as to engraft the new exclusivity provisions of 21 U.S.C. 505 onto antibiotic drugs; and, considering the probable injury to Glaxo without a decree and the likely harm to FDA and Lilly with a decree, the court denied Glaxo's motion for a preliminary injunction and temporary restraining order.

The parties pursued discovery and filed motions for summary judgment. The court granted the government and Lilly's motions for summary judgment and denied Glaxo's motion. Glaxo's entire argument rested upon a unique interpretation of 21 U.S.C. 507(e)'s transfer provisions; but the transfer provisions did not come into play without a regulation providing for exemption from batch certification. Antibiotics were exempt from batch certification only by virtue of 21 C.F.R. 433.1; and only that regulation's existence allowed Glaxo to argue that ceftazidime should be treated as a 21 U.S.C. 355 non-antibiotic drug pursuant to 21 U.S.C. 357(e). However, Glaxo had to attack such regulation as being inconsistent with Section 357(e) in order to succeed on the merits—an untenable position.

Ultimately, absent any express congressional indication to the contrary, the court refused to interpret the 1984 amendment in a manner contrary to the traditional drug approval process and in conflict with FDA's interpretation. (Misc. No. 791; S.J. No. 23)

Government Books **FOR YOU**

Take advantage of the wealth of knowledge available from your Government. The Superintendent of

Documents produces a catalog that tells you about new and popular books sold by the Government.

Hundreds of books on agriculture, business, children, energy, health, history, space, and much, much more. For

a free copy of this catalog, write—

Free Catalog

P.O. Box 37000
Washington, DC 20013-7000

