

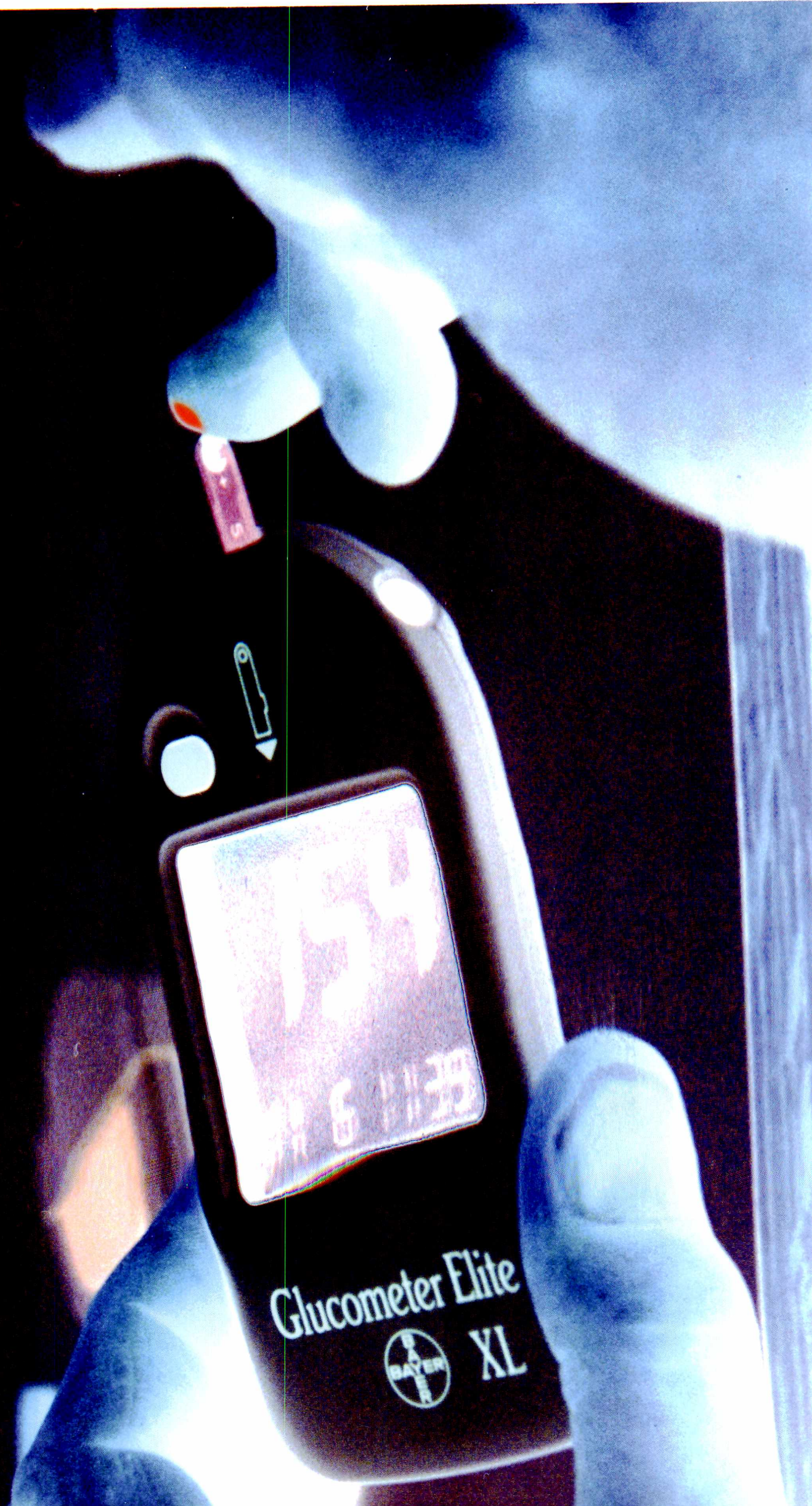
A stylized illustration of a man with a surprised expression, wearing a green tank top and blue shorts, holding a bag of snacks. He is surrounded by various food items including lobsters, eggs, a fish, corn, and a bottle of juice. The background is a warm, orange-brown color with abstract shapes.

FDA Consumer

The Magazine of the U.S. Food and Drug Administration

January–February 2002 • Vol. 36 No. 1

*Losing
Weight:*
More Than
Counting
Calories



Glucometer Elite
BAYER XL

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◀ Inside Front Cover Photo:

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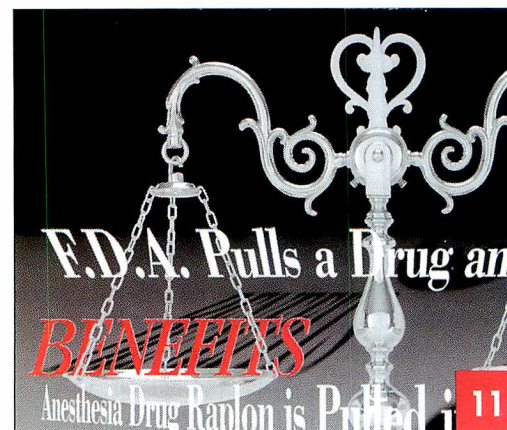
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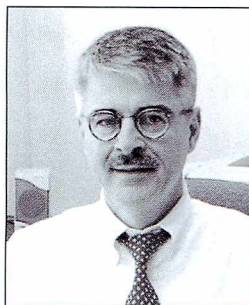
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Frequent blood glucose tests are a critical component to good diabetes care. People with diabetes test their blood glucose levels daily using a glucose meter and a drop of blood obtained using a lancet. See page 26 for more information on diabetes and the latest treatments for the disease.



Raymond Formanek Jr.

The after-effects of holiday parties, family gatherings, and too much food and drink are beginning to show on some of us. And health clubs nationwide are

gearing up for the annual influx of new members determined to jog, lift and spin off those added pounds.

New Year's resolutions and good intentions notwithstanding, excess weight and inactivity are responsible for hundreds of thousands of premature deaths each year. In fact, a recent study in the British journal *Public Health* suggests that obese adults are nearly twice as likely to have a chronic illness than adults of normal weight and that obesity is a greater risk factor for chronic illness than either smoking or drinking alcohol.

Obesity in America has risen at an epidemic rate over the past two decades.

According to the Centers for Disease Control and Prevention, 35 percent of the adult U.S. population (ages 20 to 74) is overweight. In that same population, the number of obese people—those who have an excessively high amount of body fat in relation to lean body mass—nearly doubled from about 15 percent in 1980 to an estimated 27 percent in 1999.

Reversing these trends is a priority among many concerned with public health, including governmental, voluntary and private organizations. In fact, U.S. Surgeon General David Satcher has prepared a national action plan to battle overweight and obesity. One of the objectives of the national Healthy People 2010 initiative is to reduce the prevalence of obesity among U.S. adults to 15 percent. That will not be easy. Recent studies indicate that the situation is getting worse.

For more, including the latest research on how to safely lose weight and keep it off, see our cover story this month, "Losing Weight: More than Counting Calories," beginning on page 18.

Ever wonder why drugs such as Baycol, a cholesterol-lowering drug, and Lotronex, used as a treatment for irritable bowel syndrome, get pulled from the marketplace? And just what does "safe" mean when used in the context of FDA approval of a compound? FDA experts explain the process in our article titled "Why Drugs Get Pulled Off the Market."

Diabetes is often called a "silent killer." It's the leading cause of kidney failure (end-stage renal disease) and of new cases of blindness among Americans ages 20 to 74. Diabetes, which has no cure, is the sixth-leading cause of death by disease in the United States. Find out more about this chronic condition that is affecting more and more Americans each year in our piece titled "Diabetes—A Growing Health Concern."

The *FDA Consumer* staff wishes you a happy and healthy New Year!

Raymond Formanek Jr.
Editor



First-of-a-Kind Heart Device Cleared

The FDA has cleared for marketing a first-of-its-kind pacemaker capable of transmitting data on a patient's heart condition to the doctor between office visits.

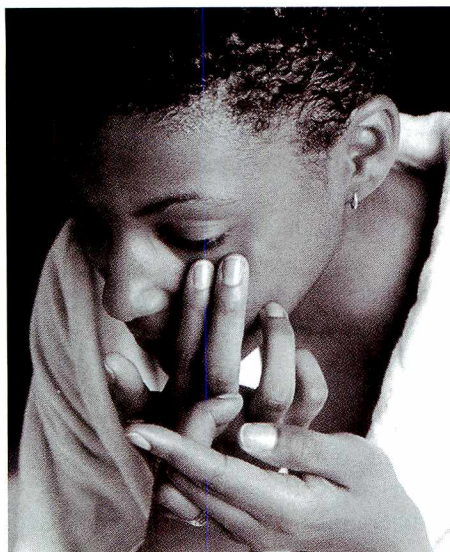
The Biotronik Home Monitoring System combines a pacemaker already on the market, a short-range radio frequency transmitter, and a cell phone-like device carried by the patient in a pocket

or handbag. The transmitter relays data from the patient's heart to the phone, which transmits it to the company's service center, where it is processed or tabulated and forwarded via fax to the physician. The device can be programmed by the physician to collect data as frequently as needed, from once a month to once a day.

The information, which can be transmitted from any location served by the manufacturer's digital cell phone pro-

vider, tells the physician how the electrical system of the heart is working and how much the pacemaker needs to work to help the heart function normally. The data is intended to supplement information gathered during the patient's regular office visits.

As with all pacemaker manufacturers, Biotronik Inc., of Lake Oswego, Ore., will be required to track the new pacemaker for the life of the product and file annual adverse event reports with the FDA.



Continuous-Wear Contact Lenses Approved

The FDA has approved a new type of soft contact lenses, safe enough to wear continuously for up to 30 nights. Prior to its approval in October, contact lenses were approved only for up to seven days of extended wear.

Focus Night and Day lenses may be worn for up to a month without removal because they allow six times more oxygen to reach the eye than current lenses.

All extended-wear contact lenses carry a greater risk of serious eye infections than lenses that are removed before retiring for the day.

The new lenses should be replaced every month, as recommended by eye-care providers, and should never be worn longer than the recommended time. When removed in between replacement times, the lenses should be cleaned and disinfected before reinsertion, or disposed of. Once lenses are removed, eyes should have a rest without lens wear for at least one night. (For more information on contact lenses, see "Vision Correction: Taking a Look at What's New" in the September–October 2001 issue of *FDA Consumer*.)

Focus Night and Day lenses are made by CIBA Vision Corp., of Duluth, Ga.

FDA Approves First Biologic Treatment for Sepsis

The FDA has approved the first biologic treatment for the most serious forms of sepsis, a life-threatening illness caused by severe infection. The new treatment, called Xigris, is a genetically engineered version of a naturally occurring human protein, Activated Protein C. It interferes with some of the body's responses to severe infection, including the formation of blood clots that can lead to organ failure and death.

"Xigris is a new treatment that helps to save the lives of patients with the most severe forms of sepsis," says the FDA's Acting Principal Deputy Commissioner Bernard A. Schwetz, D.V.M., Ph.D. "While not everyone will benefit from this treatment, we believe the approval of Xigris is an important advance for the treatment of this often deadly disease."

Of about 750,000 people who get sepsis in the United States each year, an estimated 30 percent will die from it, despite treatment with intravenous antibiotics and supportive care. Patients with severe sepsis often experience failures of various systems in the body, including the circulatory system, as well as kidney failure, bleeding, and clotting.

Xigris was approved by the FDA for the treatment of adult patients with severe sepsis who have an especially high risk of dying from sepsis, as measured by a scoring system based on their general health and the severity of their illness.

In a placebo-controlled, multi-center, randomized clinical trial of nearly 1,700 patients, the overall mortality rate was reduced by 6 percent during the 28-day study period of the trial. Among patients at higher risk of dying, the group for whom Xigris is now indicated, mortality was reduced 13 percent. The treatment did not lower mortality rates of those in the study who were less severely ill.

Because Activated Protein C interferes with blood clotting, the most serious side effect associated with Xigris therapy is bleeding, including bleeding that causes stroke. Patients at high risk of bleeding were excluded from the trial, as were severely ill patients with pre-existing conditions not related to sepsis that made them likely to die within the study period.

Xigris should not be used for patients who have active internal bleeding, or who are more likely to bleed because of certain medical conditions including recent strokes, recent head or spinal surgery, or severe head trauma.

Because sepsis is a life-threatening condition and because treatment with Xigris comes with potentially serious risks, the benefits and risks of treatment with Xigris must be carefully weighed for each individual patient.

Eli Lilly and Co., Indianapolis, will market the treatment.

We're eager to hear what you like and what you don't like.

We also want to know the subjects you'd like to see covered. Letters should be 300 words or less. If you would like your comments to be considered for publication, please sign your letter or e-mail and include your address and telephone number during business hours for verification. The editor reserves the right to edit letters for space and appropriateness.

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First Contraceptive Skin Patch

The FDA has approved Ortho Evra, the first skin patch for birth control. The prescription patch works by releasing hormones through the skin into the bloodstream to prevent pregnancy.

The square patch, just under two inches wide, consists of three layers. The hormones norelgestromin and ethinyl estradiol are embedded in the adhesive layer and are slowly released when the patch is applied to the skin.

Women using the product should apply it to the lower abdomen, buttocks or upper body, but not to the breasts. The patch is worn continuously for one week and then replaced with a new patch, for a total of three weeks of patch wear. During the fourth week, no patch is used, allowing the woman to have her menstrual period.

Like birth control pills, Ortho Evra is effective for pregnancy prevention when used as directed. The risks of using this product include an increased risk of blood clots, heart attack, and stroke. The product's warning label also notes that cigarette smoking increases the risk of serious cardiovascular side effects.

The FDA approved Ortho Evra following three worldwide clinical trials involving 4,578 women, of whom 3,319 used Ortho Evra. The other women in the trials used birth control pills. The trials demonstrated that that women were able to follow the weekly patch application and changing regimen. About 5 percent of the women had at least one patch that did not stay attached to their skin. About 2 percent withdrew from the trial due to skin irritation from the patch. The product appeared to be less effective in women weighing more than 198 pounds.

Ortho Evra was developed by R. W. Johnson Pharmaceutical Research Institute and is marketed by Ortho-McNeil Pharmaceutical Inc., Raritan, N.J. The product is sold in packages of three patches for the monthly cycle of use.

Internet Vendors Warned About Unapproved Cipro

The FDA has notified Internet vendors of foreign-made ciprofloxacin that it is taking actions to halt potentially illicit sales of the antibiotic, which has been in increased demand since recent bioterrorist attacks in the United States. Ciprofloxacin is the generic name for Cipro.

The FDA is unable to determine whether these products were made in accordance with U.S. specifications, and their sale and distribution in the United States may be illegal. Foreign-manufactured ciprofloxacin has not been approved or evaluated by the FDA, and the manufacturing practices for production of these drugs have not been regulated by the agency.

The FDA encourages consumers to be aware that several risks exist with obtaining a prescription drug over the Internet. For example, the product could be contaminated and harmful, or it could be counterfeit and not contain the drug's active ingredient. There is also the risk that foreign drugs promoted on the Internet may not be approved for marketing in this country and may not be legally imported.

Ciprofloxacin is a powerful antibiotic that should only be taken after consultation with a health-care provider. The drug is associated with side effects—some of which may be serious—and may interact with other drugs. Ciprofloxacin should not be administered to treat anthrax unless exposure to the bacterium that causes anthrax (*Bacillus anthracis*) is suspected or confirmed. Its use in the absence of suspected or confirmed anthrax exposure could result in the development of antibiotic resistance, a serious public health risk.

For more information on ciprofloxacin, visit the FDA's Web site at www.fda.gov/cder/drug/infopage/cipro/. For more information on buying drugs over the Internet or to view the cyber letters, visit the FDA's Web sites at www.fda.gov/cder/drug/consumer/buyonline/guide.htm and www.fda.gov/cder/warn/cyber/cyber2001.htm.

For additional tips on buying products online from sellers who claim their products will protect you from biological threats, see the Federal Trade Commission's consumer alert at www.ftc.gov.

FDA and the Quality and Integrity of Research

The FDA has established an office to help ensure that research studies involving humans are conducted according to good clinical practice.

Good clinical practice (GCP) is a standard for the total research process: designing studies, conducting and monitoring them, recording data, analyzing results, and reporting and submitting these results to support product applications to the FDA.

The FDA's newly established office for good clinical practice (OGCP) re-

quires that FDA-regulated medical research conform to the GCP standard.

Compliance with this standard assures that the data and reported results are credible and accurate and that the rights, safety, and well-being of people in studies are protected. "Poor quality data has an impact on the accuracy of product labels and advertising that will be used by the public—and may lead to inappropriate decision-making on product approvals," says

David Lepay, M.D., Ph.D., director of the OGCP. "Our office is out to ensure FDA's broad public protection role of high-quality decision-making on product approvals and labeling. We also



FDA Approves Viread for HIV-1 Infection

The FDA has approved Viread (tenofovir disoproxil fumarate), a new antiviral drug for the treatment of HIV-1 infection in combination with other antiretroviral medicines.

The introduction of potent antiviral drugs and the combined use of these drugs, often called “cocktails,” has markedly reduced replication of HIV in many infected people and has improved survival rates. But because HIV mutates rapidly, resistance to one or more of these potent drugs may develop over time, necessitating the development of new drugs to treat these resistant virus strains.

The FDA based its approval of Viread on two clinical studies involving more than 700 patients who had previously been treated with antiretroviral agents, but showed signs of continued HIV replication despite drug therapy.

There are no study results to show long-term inhibition of the clinical progression of HIV by Viread. In addition,

the risk-benefit ratio for people who have never been treated with antiretrovirals is unknown since the studies only included people previously treated with the drugs.

Viread is available as a 300-milligram tablet to be taken orally, with a meal. Use of the drug should be considered for adult patients with HIV strains that are expected to respond to Viread as assessed by laboratory testing or treatment history.

The most frequently reported adverse events among patients in the clinical trials were mild to moderate gastrointestinal problems, including diarrhea, nausea, vomiting and gas. Severe liver enlargement and excess fat in the liver have also occurred among patients treated with drugs similar to Viread, alone or in combination with antiretrovirals. These are severe and potentially fatal conditions.

Viread is marketed by Gilead Sciences Inc. of Foster City, Calif.

Product Problem? Report It

Health professionals can report serious adverse reactions or other product problems to the FDA’s MedWatch program by:

- Mail: Use the postage-paid MedWatch form, available from the FDA Web site or by calling the toll-free number below.
- Phone: 1-800-FDA-1088 (1-800-332-1088)
- Fax: 1-800-FDA-0178 (1-800-332-0178)
- Internet: www.fda.gov/medwatch/

Call the 800 number or visit the Web site for further assistance.

The FDA encourages consumers to report problems through their doctors, but if they prefer, they may submit the MedWatch form themselves.

want to protect subjects participating in clinical research that is critical to FDA decision-making.”

To help make sure that the GCP standard is followed, the FDA conducts more than 1,000 inspections of clinical trials each year.

The OGCP, established in October and located within the office of the FDA commissioner, works closely with the FDA centers, the FDA’s office of regulatory affairs, and the Department of Health and Human Services’ office for human research protections. The OGCP staff also works with international colleagues to implement GCP standards globally.

If you have a question about the FDA’s good clinical practice regulations and policy, call 301-827-4000 or 301-827-3340.

Drug Combination Approved for Advanced Breast Cancer

Two drugs already on the market to treat breast cancer have been approved by the FDA to be used in combination for an even greater effect in treating advanced cases of the disease.

Xeloda (capecitabine), an oral cancer therapy, and Taxotere (docetaxel), an intravenous drug, can now be used together to treat advanced cancer that has progressed after being treated with an anthracycline-containing therapy, such as Adriamycin (doxorubicin). Doctors limit anthracycline-containing treatments to life-threatening situations.

The FDA approved the drug combination in September after a study of 511 cancer patients demonstrated improvements in overall response rates, lengths of time before the disease worsened, and survival rates.

Xeloda and Taxotere individually are associated with side effects such as gastrointestinal symptoms, nausea, vomiting, and painful inflammation of the mouth. People with breast cancer also should be aware of these side effects when taking the newly approved drug combination. If side effects occur, it may be necessary to reduce the dose, or to interrupt or discontinue treatment.

In addition, Xeloda has a significant drug interaction with oral coumarin-derivative anticoagulant therapy, which can cause serious bleeding complications. The FDA urges people receiving Xeloda and a coumarin-derivative, such as Coumadin, to have their anticoagulant response monitored frequently. The agency also says that dosages of the drugs may have to be modified for people who have impaired kidney function.

Xeloda is manufactured by Roche Laboratories Inc., Nutley, N.J. Taxotere is marketed by Aventis Pharmaceuticals Inc., Bridgewater, N.J.

Home Male Infertility Test

The first male infertility home test kit available without a prescription has been cleared for marketing by the FDA. The test indicates when sperm cell counts fall below a certain level—a potential indicator for male infertility.

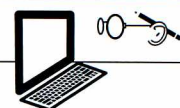
The FertilMARQ Home Diagnostic Screening Test for Male Infertility

stains cells in the sperm sample to produce a color. The color is then compared to a reference (chart/guide) on the test kit. The color comparison tells the user whether the sperm cells in the sample are positive—above 20 million per milliliter (/mL) or negative—below 20 million/mL. However, because this is a screening test, a positive test is no guar-

antee of infertility, meaning that other factors may be involved. Users should confirm test results with their physicians.

Embryotech Laboratories Inc., of Wilmington, Mass., makes the FertilMARQ test kit, which was cleared for marketing in August.

RESEARCH NOTEBOOK



Study: Aspirin and Warfarin Equally Effective for Stroke Prevention

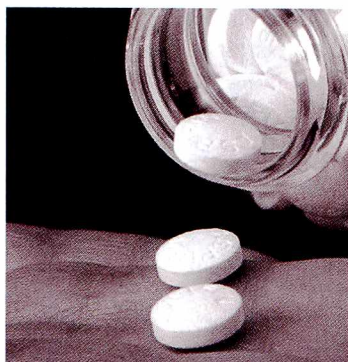
Stroke is the third leading cause of death in the United States and the leading cause of serious, long-term disability. About 600,000 new strokes are reported in the United States annually and about 160,000 Americans die each year from stroke.

A study appearing in the Nov. 15, 2001, issue of *The New England Journal of Medicine* indicates that aspirin works as well as warfarin in helping to prevent recurrent strokes in most patients.

The study, called Warfarin versus Aspirin Recurrent Stroke Study (WARSS) was a seven-year double-blind, randomized clinical trial involving 2,206 patients at 48 participating centers—the largest trial to date comparing aspirin to warfarin for recurrent stroke prevention. It was sponsored by the National Institute of Neurological Disorders and Stroke (NINDS).

“Treatment is far superior to no treatment and treatment with either aspirin or warfarin is safe under carefully monitored conditions,” says J. P. Mohr, M.D., director of the stroke unit at Columbia University’s College of Physicians and Surgeons and lead investigator of the trial.

Both drugs slow clotting of the blood, and blood clots are involved in the final stages of the most common type of



stroke due to blockage of the vessels that supply oxygen-rich blood to the brain. Aspirin affects the blood platelets, while warfarin inhibits circulating clotting proteins in the blood.

Aspirin has been used for over 100 years, but its beneficial effects to prevent stroke and heart attack only started to be recognized in the 1970s. Whether warfarin was superior to aspirin for stroke prevention was unclear prior to WARSS. Numerous previous studies have proven that use of aspirin reduces recurrent stroke by about 25 percent.

Part of the controversy about aspirin versus warfarin for stroke prevention has been the thinking among physicians. Many say that warfarin may be a better blood thinner than aspirin to prevent almost all forms of stroke, but add that it has greater side effects, increased risk of hemorrhage, and higher costs due to the need for blood tests to monitor the treatment effect.

An earlier NINDS trial cleared up some of the confusion by showing a distinct benefit of warfarin over aspirin in preventing recurrent stroke in patients whose stroke was related to atrial fibril-

lation (AF)—strokes caused by clots coming from the heart. About 15 percent of stroke patients have this heart rhythm abnormality, a condition in which the two upper chambers of the heart (the atria) do not have a rhythmic, forceful beat and the pulse is irregular.

However, greater insight was needed to determine the best therapy in preventing recurrent stroke in the larger number of patients without clots in the heart—the purpose of the WARSS study.

To make the aspirin and warfarin arms of the study as unbiased as possible, the investigators matched both groups of patients for primary stroke severity, age, gender, education, and race/ethnicity. The two groups were also matched for stroke risk factors, including hypertension, diabetes, cardiac disease, smoking, alcohol consumption, and physical activity.

The investigators used an aspirin dose of 325 milligrams per day and a warfarin dose specifically tailored to each individual patient. They also used a double-blind plan in which neither the treating doctor nor the patient knew which treatment was being received.

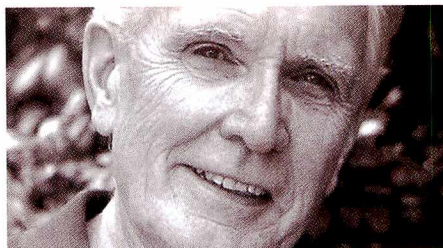
The researchers say additional analysis of the WARSS data may point to differences in the ability of aspirin and warfarin to prevent stroke for some patients. However, there was no evidence of significant differences overall between the two drugs.

A Smile a Day May Help Keep Heart Disease Away

Older men who see life's glass as being half full rather than half empty may be less likely to develop coronary heart disease, a new study indicates.

Researchers ranked a group of more than 1,000 older men based on a scoring system that characterized them along a continuum from pessimist to optimist. They found that each step up the scale toward optimism decreased the risk of coronary heart disease (CHD). The men ranked as being most optimistic had a risk of heart disease less than half of that of those ranked the most pessimistic, according to a study published in the November–December 2001 issue of *Psychosomatic Medicine*.

"These ... data are among the first to demonstrate that a more optimistic [per-



spective], or viewing the glass as half full, lowers the risk of CHD in older men," says lead author Laura D. Kubzansky, Ph.D., of the Harvard School of Public Health.

The study is based on data from 1,306 men whose average age at enrollment was just over 60 and who were followed for an average of 10 years.

Despite the protective effect on the development of CHD, the optimistic men were no less likely to die of any cause than were pessimistic men in the

study. This may have been related to the fact that all the men, as veterans, had ready access to health care through the Department of Veterans Affairs, reducing their risk of dying from heart disease, according to the study.

The researchers suggest that the protective effects of optimism may be, in part, due to lower stress, which has been shown to decrease heart disease risk. Also, optimists are more likely to engage in health-promoting activities such as exercising and not smoking. However, the researchers note that their findings pertain specifically only to white men and cannot be generalized to women or non-white men.

The study was supported with funding from the National Heart, Lung, and Blood Institute and the National Institute on Aging.

Study: Treatment Reduces Risk of Heart Attack by 70 Percent

Cardiovascular disease is the No. 1 killer in most industrialized countries. A new study indicates that combining the use of a statin drug and niacin can reduce the risk of heart attack or hospitalization for chest pain by 70 percent among people likely to suffer heart attacks and/or death from coronary heart disease.

The treatment used in the study combined two well-known ways of improving cardiac health: the use of a statin drug called simvastatin to lower levels of the so-called "bad" cholesterol, LDL, and the use of niacin, also called vitamin B-3, to boost levels of the "good" cholesterol, HDL. Niacin is the best agent known to raise blood levels of HDL, which helps remove cholesterol deposits from the artery walls.

The study, done by researchers at the University of Washington and published in the Nov. 29, 2001, issue of the *New England Journal of Medicine*, found that the combined treatment, in people with low levels of HDL and average levels of LDL, could even reverse plaque buildup in the arteries.

"This study shows that improving cholesterol levels in people with heart disease—especially lowering LDL cholesterol substantially, together with raising HDL cholesterol—greatly reduces the risk for a heart attack and heart disease complications and can actually reverse the buildup of cholesterol in the arteries of the heart," said Claude Lenfant, M.D., director of the National Heart, Lung, and Blood Institute, which funded the study.

Researchers also looked at the effect of a mixture of antioxidant vitamins on cardiovascular outcomes. The antioxidants involved in this study include vitamins C and E, beta-carotene and selenium.

The study found that the mixture of antioxidant vitamins actually blunted the expected rise in the "good" HDL cholesterol usually seen with the simvastatin and niacin combination. Scientists are not sure why this is so, since there has been laboratory evidence that suggests antioxidants should be helpful.

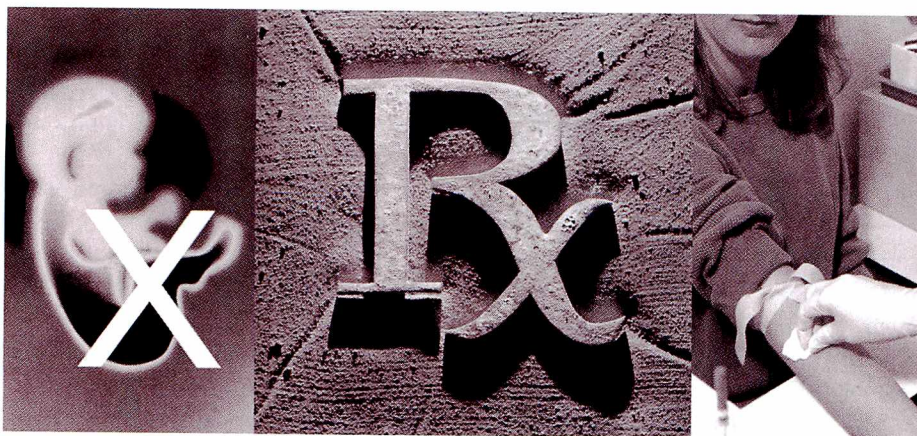
At the start of the study and again af-

ter three years of treatment, doctors performed angiograms on the arteries of the 160 people in the study. The angiograms, using computerized measurements, showed that in most of the people who received the combination treatment, plaque buildup had actually decreased.

"This is the first demonstration of a striking clinical benefit from this form of combination drug therapy used in patients with a common type of coronary disease," says B. Greg Brown, M.D., lead author of the study and a cardiologist at the university's medical school.

Giving statins to people with cardiovascular disease is now common, and has been proven to reduce cardiovascular risk by 25 percent to 35 percent over five years of treatment. The study involved use of niacin at moderately high and carefully supervised levels. Brown said that patients should only take niacin under a doctor's supervision. Rarely, the unsupervised use of niacin can cause severe liver problems, including liver failure.

Accutane Risk Management Program Strengthened



The Food and Drug Administration has announced changes that strengthen a risk management program regarding pregnancy and a drug used to treat severe acne. Accutane (isotretinoin) is a drug approved to treat the most serious form of acne—a type that is painful, permanently disfiguring, and does not respond to other acne treatments. Accutane is very effective, but its use carries significant potential risks, including birth defects and even fetal death.

The new risk management program is called S.M.A.R.T., the System to Manage Accutane-Related Teratogenicity. “Teratogen” refers to any substance with the potential to cause birth defects. S.M.A.R.T. was developed in consultation with the FDA by Accutane’s manufacturer, Roche Laboratories of Nutley, N.J. The program is designed to enhance safe and appropriate use of the drug by strengthening an existing patient education program known as the Accutane Pregnancy Prevention Program.

In recent years, as more and more women have been receiving Accutane prescriptions, the risk that pregnant women may be inappropriately using the drug has increased. In September 2000, the FDA held a meeting of its dermatologic and ophthalmic drugs advisory committee to discuss what additional measures might help prevent exposure of unborn babies to Accutane.

The S.M.A.R.T. program was developed to address the two main goals identified at the meeting. The first is that no

woman should begin Accutane therapy if she is pregnant; and second, no pregnancies should occur while a woman is taking Accutane.

The risk management components are described fully within the boxed contraindications and warnings (Black Box) and the precautions sections of the Accutane package insert, which provides prescribing information for health-care professionals. The S.M.A.R.T. program requires the following:

- Doctors who prescribe Accutane must study the S.M.A.R.T. “Guide to Best Practices” provided by Roche, and then sign and return to Roche a “Letter of Understanding” certifying their knowledge of the measures to minimize fetal exposures to Accutane. The manufacturer has also developed a continuing medical education (CME) course for Accutane prescribers that includes specific, practical information about pregnancy prevention. The FDA strongly encourages participation in this half-day course. Accutane prescribers will then receive special self-adhesive Accutane qualification stickers from Roche. All Accutane prescriptions should have the special yellow sticker attached to the prescriber’s regular prescription form. This sticker will indicate to the pharmacist that the patient is “qualified” according to the new package insert. This means the patient has had negative pregnancy tests as described below, as well as education and counseling about pregnancy prevention. The pregnancy test

will be repeated every month throughout the Accutane treatment course, and no prescriptions should be given for more than a one-month supply of Accutane at a time.

- All female patients must have two negative urine or serum pregnancy tests before the initial Accutane prescription is written. And for each month of therapy, they must have a negative pregnancy test result before receiving their next prescription, regardless of whether they are sexually active. Patients who are, or who might become, sexually active with a male partner must also select and use two forms of effective contraception simultaneously for at least one month before initiation of Accutane therapy, during therapy, and for one month following discontinuation of therapy, according to the program. They must sign a patient information/consent form about Accutane and birth defects, in addition to the consent form that all patients should receive about other potentially serious risks related to Accutane. Finally, female patients must be given the opportunity to enroll in the Accutane survey. This confidential survey will collect data to help Roche and the FDA decide if S.M.A.R.T. is helping to prevent exposure of unborn babies to Accutane.

- Pharmacists will dispense Accutane only upon presentation of a prescription with the special Accutane qualification sticker. Pharmacists will dispense a maximum one-month supply of Accutane, fill prescriptions within seven days from the date of “qualification” and provide a medication guide for patients with each Accutane prescription. Requests for refills and phoned-in prescriptions will not be filled.

Exposure of an unborn baby to Accutane is a serious adverse event and should be reported to Roche Medical Services at 1-800-526-6367 or the FDA MedWatch program at 1-800-FDA-1088 (1-800-332-1088). MedWatch can also be accessed via the Internet at www.fda.gov/medwatch/. ■

Teen Science Classes

Serve Up Lessons In Food Safety

Every year 76 million Americans experience a foodborne illness; 325,000 are hospitalized and 5,000 die, according to the Centers for Disease Control and Prevention. In response to this public health concern, the Food and Drug Administration and the National Science Teachers Association teamed up to create a first-of-its-kind science program to teach teen-agers about food safety.

The program, dubbed *Science and Our Food Supply*, is offered free to science educators and is the largest public education program developed to teach middle and high school students about food safety and food science careers. It can be incorporated into biology, life sciences, and other science classes. Teacher guides for middle level and high school educators each contain 16 hands-on experiments and activities presented in five modules:

- Understanding Bacteria
- Farm, Processing and Transportation
- Retail and Home
- Outbreak
- Future Technology

The modules offer lessons on bacterial growth and how pathogens pose a risk of causing illness; how practices on the farm, such as safe composting, can lead to safer crops; how food processing technologies such as ultra high temperature pasteurization are leading to new products; and how safe food handling practices in restaurants and at home can reduce foodborne illness.

"Since Americans now spend half of their food dollars on food prepared by others like take-out and restaurant meals, it is critical that food eaten outside the home is safely prepared," says Joseph A. Levitt, director of the FDA's

Center for Food Safety and Applied Nutrition (CFSAN).

"Another reason for targeting a food safety program to teens," Levitt says, "is that more high school students are employed in restaurants than any other industry, yet they often begin their jobs with little information about food safety and ways they can prevent foodborne illness."

Science and Our Food Supply offers students hands-on activities based on good scientific methods and laboratory practices. In one experiment, students observe, record and graph bacterial growth in hamburgers that they cook to various temperatures. Another experi-



Dustilynn Benny, a Baltimore middle school student, helps test milk quality during a press conference promoting an educational program aimed at teaching students the basics of food safety. The free program was developed jointly by the FDA and the National Science Teachers Association.

ment helps students understand the pasteurization process by having them test and compare unpasteurized and pasteurized fruit juice.

To reinforce activities and experiments, the program includes a 46-minute video called *Dr. X and the Quest for Food Safety*, which recently won an Emmy award from the National Academy of Television Arts and Sciences Mid-Atlantic Region in the category of "Outstanding Children's Program/One-time Only Special." The video features a savvy food scientist who leads students on a journey through the food supply chain, exploring behind-the-scenes research in laboratories and profiling scientists in food safety careers. Also included is a *Food Safety A to Z Reference Guide* with frequently asked questions, fun facts, and tips.

Professional development workshops are available to middle level and high school science educators on how to incorporate *Science and Our Food Supply* into the curriculum. Teachers also have opportunities to tour FDA research facilities and work with FDA scientists to learn the latest on food science research. One hundred teachers have participated so far and more will be invited to participate this summer. Applications for this program are being accepted until March 1, 2002. More information and an application form are

available on the NSTA Web site at www.nsta.org/fda.

To receive a copy of the *Science and Our Food Supply* program, teachers can complete a request form on the NSTA Web site at www.nsta.org/professionalinfo. Teachers can also mail requests to NSTA, *Science and Our Food Supply*, 1840 Wilson Boulevard, Arlington, VA 22201-3000, or fax to 1-888-433-0526. ■

Bringing Real Life To The Table

Patient Reps Help FDA Review Products

By Michelle Meadows

When Jim Anderson of La Plata, Md., became an FDA patient representative in 1997, he wasn't sure how much help he could be. In preparation for his first advisory committee meeting, the Food and Drug Administration sent him a new drug application (NDA) briefing package, which he describes as "10 pounds of paper."

"I couldn't pronounce half the words," he says, "and I was scared to speak ..."

But the fear didn't last long, says Anderson, who was diagnosed with prostate cancer in 1993. He recalls reviewing a drug that gave "a small chance to provide pain relief and a significant risk of heart failure," in his opinion. He was glad he spoke up about it because his concern prompted a serious discussion among the scientists and doctors.

Anderson was one of about 23 patient representatives who gathered in Rockville, Md. for an FDA training workshop in September. Since 1991, patient representatives have served on FDA advisory committees to help review products. Advisory committees provide a forum through which the FDA seeks advice from outside experts and consumers.

Patient representatives give the FDA and its advisory committees insight on issues and questions important for patients and family members living with serious and life-threatening illnesses. The patient representative program began after Congress passed legislation requiring consumer representation on advisory committees and HIV/AIDS advocates demanded to be included on advisory committees that review products affecting their lives. Over the years, the FDA saw the significant contribution HIV/AIDS patients made to the regulatory review process, and the distinct category of patient representatives was expanded to include other committees.

FDA experts in the areas of drugs, radiological health, medical devices, and biologics briefed those at the workshop on the agency's product review process.



FDA patient representative Jim Anderson

Among the workshop agenda topics was how to sift through the hefty NDA applications, which contain results from animal studies, clinical tests, and other drug information. Patient representatives should expect to spend at least 10 hours reviewing the material before an advisory committee meeting.

Patient representatives typically have experience with and are knowledgeable about a specific serious or life-threatening illness. They also typically have a formal affiliation with a patient advocacy organization. About 60 patient representatives now serve on the FDA's 32 advisory committees.

Most patient representatives serve on committees that review products related to HIV/AIDS and cancer. But additional diseases, such as arthritis, diabetes, lupus, and Parkinson's disease, are also included. Patient representatives are reimbursed for travel, lodging, and daily expenses. A modest honorarium is provided for each day of service at the meeting.

Critical Questions

During the fall workshop, Steven

Hirschfeld, M.D., Ph.D., a medical officer in the FDA's division of oncology drug products, described the challenge of pinpointing the indicators that reasonably predict whether a drug will have a benefit. "When it comes to approving a drug's use, you want to prolong someone's life, make it better, or both," Hirschfeld says. "The hard part is figuring out what and how you can determine what 'better' means. A change in the size of tumor nodules may or may not have a benefit."

Hirschfeld advises patient representatives to make a list of the questions they think are critical and then work to find the answers in the NDA briefing documents. Typical questions include: What are the claimed benefits? How durable is the benefit? What are the risks? Are the patients in these studies representative of the typical patient? Does the data prove what the company claims it does or is it just interesting data that indicates the need for further research? Then, he says, make a list of the answers to these questions, with both the company analysis and the FDA analysis side by side. Such a list helps patient representatives

focus on what questions and points to bring up during the meeting.

"Ask the hard questions" of the pharmaceutical companies and of the FDA analysis, Hirschfeld says. Some common problems with NDA submissions are incomplete data and multiple terms for the same type of adverse event. An event may be described as "liver toxicity" in one section and "right upper quadrant pain" in another. Another thing to watch for, he says, is a claim after the fact of an unexpected benefit. For example: "It didn't shrink tumors after all and it did not prolong life. But the people in the study felt their memory improved." This may be an important observation for the design of a future study, Hirschfeld says, "but it should not be construed as the basis for approval of the application under review."

Anderson says, "Over the last five years, I have become more sensitive to what a big job FDA has." He has also been selected for the FDA's cancer drug development patient consultation program, a recent extension of the patient representative program. The consultation program is a joint effort between the FDA's office of special health issues and division of oncology drug products. Its goal is to bring patients into the drug development process earlier than at the advisory committee level, which comes later.

Hirschfeld says, "No one else will have the experience and perspective of a patient familiar with a disease to determine if a benefit is meaningful or if the burden is severe." According to Hirschfeld, patient representatives don't need to be statisticians. "The idea is that you pick out key points, ask whether there is a benefit that justifies the risk, and make your point of view known," he says. "And don't be seduced by an eloquent speaker with color slides—from either the pharmaceutical company or the FDA." ■

For more information on the patient representative program, write to the FDA's Office of Special Health Issues (HF-12), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4460. Or, visit the Web site www.fda.gov/oashi/patrep/patientrep.html.

Why Drugs Get Pulled Off The Market

By Michelle Meadows

"But aren't drugs supposed to be safe?"

According to Janet Woodcock, M.D., director of the Food and Drug Administration's Center for Drug Evaluation and Research (CDER), people tend to ask that question a lot when a drug is taken off the market. The FDA's mission is making sure that drugs are "safe and effective." So what does "safe" really mean?

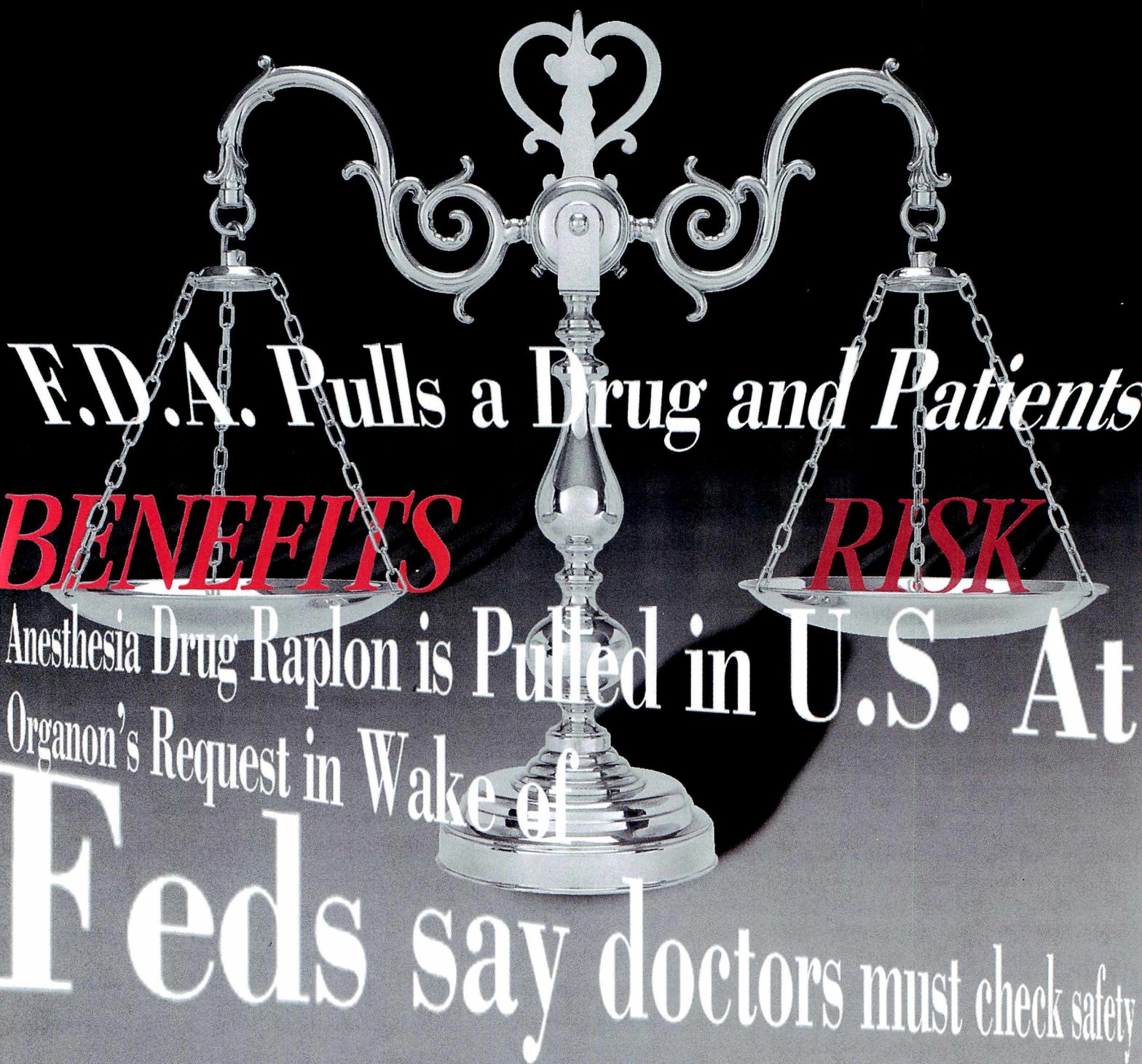
When it comes to any drug, "safe" means that the benefits of the drug outweigh the risks for the population the drug is intended to treat and for its intended use. "Safe does not mean harmless," Woodcock says. "Every drug comes with risks, and our tolerance for risk is higher for drugs that treat serious and life-threatening illnesses. There is no question that cancer drugs can be highly toxic. But they also save lives."

If the FDA decides that a drug's benefits outweigh its risks, the agency approves the drug for marketing. Approved drugs continue to be evaluated through postmarketing surveillance—a system that monitors a drug's safety on an ongoing basis. Postmarketing surveillance seeks to identify problems that weren't observed or



Janet Woodcock, M.D.

Every drug comes with risks, and our tolerance for risk is higher for drugs that treat serious and life-threatening illnesses.



F.D.A. Pulls a Drug and *Patients*

BENEFITS *RISK*

Anesthesia Drug Raplon is Pulled in U.S. At Organon's Request in Wake of

Feds say doctors must check safety

ILLUSTRATION BY JESSE NICHOLS JR.

The critical question is: Do the benefits of this drug still outweigh its risks for the population described in the labeling?

recognized before approval and any problems that might arise because a product isn't being used as anticipated.

The goal is to catch any bad news right away so that the FDA and drug companies can act quickly and communicate new risk information to consumers and doctors. CDER evaluates required reports from drug companies, which must promptly pass on any report they receive of a serious adverse reaction that isn't already described in the drug's labeling. CDER also relies on MedWatch, the system through which consumers and health professionals voluntarily report adverse events associated with all products the FDA regulates.

When the FDA receives reports of significant new adverse events, the agency evaluates them for their seriousness and the likelihood that they were caused by the drug. To the extent possible, the agency also considers how the toxicity compares with other treatments for the same disease. Ultimately, of course, the critical question is: Do the benefits of this drug still outweigh its risks for the population described in the labeling? In many cases, that question cannot be answered immediately, and more reports must be considered. Sometimes, the impact of labeling revisions needs to be assessed.

Usually, when important new risks are uncovered, the risks are added to the drug's labeling and doctors are informed of the new information through letters and other education. It's only rarely that the approval decision on a drug needs to be reassessed and changed. A conclusion that a drug should no longer be marketed is based on the nature and frequency of the ad-

verse effect and how the drug compares with treatment alternatives.

When the FDA believes it is clear that a drug no longer has a place in treatment, it will ask the manufacturer to withdraw the drug voluntarily. Companies have agreed to withdraw the drug in all cases except one—the case of an antidiabetic drug called phenformin, which was taken off the market in 1976 as an imminent hazard, despite the company's objections. If a company does not agree, the FDA can bring formal procedures to require withdrawal.

At first glance, one might assume that every time a drug comes off the market, it means that somewhere along the way somebody made a horrible mistake—that the drug never should have been on the market in the first place. But FDA experts say that would not be correct. Most often, the withdrawal occurs because of adverse effects that were not seen prior to marketing. Sometimes, there was no clue at all. In other cases, one can see hints of the problem in retrospect, but not the serious events that eventually led to the withdrawal.

Many complex factors go into making judgments about benefits and risks, and into ultimately deciding whether a drug should be taken off the market. Here are some major issues, often overlapping, that weigh into the decision-making process.

Rare, Unpredictable Problems

Most drugs on the market are well-tolerated and their adverse effects are known. Known side effects cause more injuries and deaths than unrecognized side effects. But some problems happen so infrequently that they can't be seen or predicted before a drug gets on the mar-

ket. Serious drug-induced liver disease, for example, is the leading single reason drugs have been pulled from the market. But it is rare, occurring at a rate of 1 in 5,000 to 1 in 10,000 exposures or less. This will not show up in clinical trials, which will pick up relatively common problems.

"If we want reasonably rapid access to needed drugs, it's not practical to require that they be tested in 15,000 to 30,000 people, which is what you'd need to be reasonably sure you saw even one case that occurs at a rate of 1 in 5,000 to 10,000," according to Robert Temple, M.D., director of the FDA's office of medical policy. "And the case would need to be recognized as drug induced," he says. So drugs are typically tested in several thousand subjects, allowing detection of relatively common serious adverse events, such as those affecting 1 in 1,000 people. This practical size of clinical trials means we can't know everything about a drug when it gets on the market. Rare events will only surface when the drug is used in larger numbers of people. Temple says, "Sometimes less severe events that are seen in trials can be used to predict the occurrence of rare, more serious events, but that is not always the case, and such predictions have considerable uncertainty."

The number of subjects in clinical trials is increasing in some areas of drug development, says Peter Honig, M.D., director of the FDA's office of drug safety. "But the numbers will never be large enough to eliminate the need for postmarketing surveillance." The FDA is working on ways to better predict rare events, especially those related to the liver and heart. But some uncertainties will always be there, including the pos-

It's a rare occasion when a drug is taken off the market.

sibility of rare characteristics that make some people particularly susceptible to an adverse reaction.

More Toxic than Expected

There are also times when a drug's toxicity is known, but the drug turns out to be more toxic than the clinical trials suggested, which again may only be seen when the drug is used in larger numbers or in different ways.

Initially approved in 1997, Baycol (cerivastatin) was a member of a class of cholesterol lowering drugs known as "statins." Baycol and the other five drugs in its class—Lipitor (atorvastatin), Lescol (fluvastatin), Mevacor (lovastatin), Pravachol (pravastatin), and Zocor (simvastatin)—have all been associated with rare reports of rhabdomyolysis, a condition that causes marked breakdown of muscle cells and can sometimes lead to fatal kidney failure and other problems.

Knowing this about the statin drugs, the FDA made sure to look for the problem when deciding to approve Baycol. But the agency didn't find unusual risk associated with the drug at that time. "In its first few years, Baycol had a small market share," says Sandra Kweder, M.D., acting director of the FDA's office of review management. "But when FDA approved a higher dose of the drug after initial marketing, use of the drug grew and we could see clearly that Baycol caused the problem more frequently than the other drugs in its class." Problems with Baycol were reported most frequently when it was used at higher doses, when used in elderly patients, and particularly, when used with another lipid-lowering drug called Lopid (gemfibrozil). Baycol was voluntarily withdrawn in the summer of 2001.

When Safer Options Are Available

When the FDA approved Seldane

(terfenadine) in 1985, the drug became the first prescription antihistamine to relieve allergies without causing drowsiness—a side effect that can cause accidents and injuries. A few years after approval, it was discovered that Seldane could cause fatal heart rhythm irregularities when it was used together with drugs that slowed its elimination from the body, or in patients with liver disease.

Major efforts to warn against use in such patients were partly successful, but fatal rhythm abnormalities continued to be reported. According to Temple, removal of the drug was considered, but that would have left only one non-sedating antihistamine, so Seldane remained available.

"But the equation shifted when Allegra came on the market in 1997," Temple says. "Allegra provided exactly the same benefits of terfenadine but without the risk of the potentially fatal heart condition." So the new availability of Allegra (fexofenadine) weighed heavily in the decision to withdraw Seldane.

Dangerous Combinations

Like Seldane, a heart drug called Posicor (mibefradil) posed problems mainly when used with other drugs. Although Posicor itself did not have unusual toxicity, it was taken off the market in 1998 because of its interactions with at least 25 drugs. It markedly increased the blood levels of those drugs, leading to potentially fatal side effects of the other medications.

When Posicor was first marketed in 1997, its labeling warned of possible interactions with three drugs. Two more drugs were later added, but reports of interactions and resulting adverse reactions with even more drugs kept coming. There was concern over whether it was realistic to expect physicians to be able

to use Posicor safely, given the many drugs it interacted with. In the absence of any special benefit of Posicor compared to other members of its class, such as effectiveness in people who don't respond to other treatments, the FDA concluded that the drug should be removed from the market.

When taken at a higher than recommended dose and when taken with other drugs, Hismanal (astemizole), another non-sedating antihistamine approved in 1988, posed risks similar to Seldane. The drug was withdrawn in 1999, as safer alternatives became available.

Beginning about 1990, many potentially harmful interactions between drugs and even between drugs and foods (such as grapefruit juice) were noted with Seldane and other drugs. The discovery led to greater attention by the FDA and drug manufacturers to such interactions before drugs are marketed, Temple says. This represents a significant enhancement of safety assessment.

Improper Use

The term "safe" also depends on whether a drug is used according to the labeling. This is why the FDA makes sure labeling and advertising for prescription drugs are accurate and balanced—presenting both the benefits and the risks.

The major problem with Duract (bromfenac), a nonsteroidal anti-inflammatory drug, was that the directions were not followed. The pain drug was withdrawn in 1998 after liver failure occurred in patients who took the short-term treatment for pain for more than the 10 days recommended in the labeling. Clinical trials indicated that a higher incidence of elevated liver enzymes was associated with longer use. Duract's manufacturer, Wyeth-Ayerst Laboratories, Philadelphia, added a new warning
(Continued on page 17)

Myths About Drug Withdrawals And User Fees

During the 1980s and early 1990s, the FDA was criticized for taking too long to review and approve drugs. Then Congress, the FDA, and the pharmaceutical industry negotiated the Prescription Drug User Fee Act (PDUFA) of 1992. Under PDUFA, drug companies pay fees that allow the FDA to add more resources and speed up drug review time.

The FDA agreed to complete its review of marketing applications within specific times. For example, by 2002, the FDA's reviews of all marketing applications for new drugs were to be completed within 10 months. PDUFA allowed the agency to have a 60 percent increase in staff assigned to review new drug applications. The agency has essentially met all review-time goals. The faster review has led to more rapid approval, with median approval time cut in half—from about 30 months to 15 months. PDUFA was extended through 2002 by the FDA Modernization Act of 1997.

Myth #1: Drug withdrawals have become increasingly common because ever since user fees, the FDA has sped up drug approvals so much that mistakes are slipping through.

The reality is that it's a rare occasion when a drug is taken off the market. The FDA is the consumer watchdog for the more than 10,000 drugs on the market, and the drug withdrawal rate has been essentially constant over the last two decades. And when comparing the time before user fees and after, there has been no change in the rate of drug withdrawals, says Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research. "There was a cluster of withdrawn drugs in 1997

and 1998, but if you look at the number withdrawn as a percent of those approved for each year, the rate was about 2.7 percent before user fees and is about 2.8 percent after user fees." Some of those drugs withdrawn in 1997 and 1998 had been on the market long before user fees took effect.

Faster reviews to get valuable and life-saving drugs on the market does not translate into safety shortcuts. It isn't that the same number of FDA reviewers are working faster. It also isn't the case that shorter FDA review times mean abbreviated clinical drug trials.

Myth #2: User fees make it difficult for the FDA to stay neutral.

FDA experts say PDUFA has clearly created a situation in which the FDA is responding faster to applications and is having more discussions with drug companies.

The FDA and drug companies share a common interest in getting drugs that are safe and effective to the market and in conducting well-designed trials that are persuasive. "We believe the many meetings and other forms of advice that we give help assure that," says Robert Temple, M.D., director of the FDA's office of medical policy. "Naturally, once they submit an application, the companies want our answer to their drug application to be 'Yes,'" he says, "but we are completely neutral, having no preferred answer except the right one." The FDA's mission is to protect the public health fairly and consistently. Decisions are scientifically-based, not influenced by user fees. ■

—M.M.

Safety-Based Drug Withdrawals (1997-2001)

Drug Name	Use	Risks	Date Approved	Manufacturer
2001				
Baycol (cerivastatin)	Cholesterol drug	Risk of rhabdomyolysis, severe damage to muscle that is sometimes fatal, especially when used at a high dose or with another drug called gemfibrozil	1997	Bayer Pharmaceutical Division, West Haven, Conn.
Raplon (rapacuronium bromide)	Injectable anesthesia drug administered as a muscle relaxant for breathing tube placement and surgery	Risk of bronchospasm, an inability to breathe normally that can lead to permanent injury or death	1999	Organon Inc., West Orange, N.J.
2000				
Lotronex (alosetron)	Treatment for irritable bowel syndrome in women	Risk of intestinal damage resulting from reduced blood flow to the intestine (ischemic colitis) and severely obstructed or ruptured bowels (complications of severe constipation)	2000	Glaxo Wellcome Inc. (now GlaxoSmithKline), Research Triangle Park, N.C.
Propulsid (cisapride)	Treatment for nighttime heartburn	Risk of fatal heart rhythm abnormalities	1993	Janssen Pharmaceutica Inc., Titusville, N.J.
Phenylpropanolamine	Decongestant used in many prescription and over-the-counter cough and cold medications	Risk of hemorrhagic stroke (bleeding in the brain)	**	**
Rezulin (troglitazone)	Treatment for type 2 diabetes	Risk of severe liver toxicity	1997	Parke-Davis/Warner Lambert, Morris Plains, N.J.
1999				
Hismanal (astemizole)	Antihistamine	Risk of fatal heart rhythm abnormalities when used with other drugs or at too high a dose	1988	Glaxo Wellcome Inc. (now GlaxoSmithKline)
Raxar (grepafloxacin)	Antibiotic	Risk of fatal heart rhythm abnormalities	1997	Glaxo Wellcome Inc. (now GlaxoSmithKline)
1998				
Posicor (mibefradil)	Treatment for high blood pressure and chronic stable angina	Risk of dangerous interactions with other drugs	1997	Roche Laboratories, Nutley, N.J.
Duract (bromfenac)	Pain reliever	Risk of severe liver damage	1997	Wyeth-Ayerst Laboratories, Philadelphia
Seldane (terfenadine) and Seldane-D	Antihistamine	Risk of fatal heart rhythm abnormalities	1985	Hoechst Marion Roussel, Kansas City, Mo., and Baker Norton Pharmaceuticals, Miami
1997				
Pondimin (fenfluramine)	Treatment for obesity	Risk of heart valve abnormalities	1973	Wyeth-Ayerst Laboratories
Redux (dexfenfluramine)	Treatment for obesity	Risk of heart valve abnormalities	1996	Wyeth-Ayerst Laboratories

** Phenylpropanolamine was in use prior to 1962, when an amendment to food and drug laws required a review of the effectiveness of this and other drugs while they remained on the market. It was deferred from final approval because of safety concerns about a possible association between phenylpropanolamine use and an increased risk of stroke. Based on previous case reports of stroke and data from a recent safety study, the FDA is proposing to remove phenylpropanolamine from the market.

Restricted Distribution

A variety of means have been used to limit distribution of particularly dangerous drugs to be sure they are being used safely, and in some cases, to direct use to the right people.

Propulsid (cisapride) was taken off the market in 2000 because of the risk of heart rhythm abnormalities, but it is still available under a special kind of investigational use. The drug is available to people with severely debilitating conditions for whom the benefits may outweigh the risks and who meet specific clinical eligibility criteria. This limitation assures that it will not be given to people who don't really need it.

In some cases, it is clear that assuring safety will require strict limitations from the outset. Thalidomide was studied in the late 1950s as a sleeping pill and as a treatment for morning sickness in pregnancy, but was not marketed in the United States. The drug is well known for causing severe birth defects. It was approved in 1998, but it is only available under a very restricted distribution system to assure that fetuses are not exposed to it. Thalidomide is labeled for use to treat painful and disfiguring skin sores associated with Hansen's disease (leprosy), but has other potentially important uses under development.

It is absolutely essential that this system work, says Robert Temple, M.D., director of the FDA's office of medical policy. "If people didn't follow the directions while taking thalidomide, the consequences would be terrible," he says. "But it is working and people do follow directions."

In some cases, a drug is marketed generally, but proves to have such a serious effect that it has to be considered for restricted distribution. A critical factor in such cases is whether the FDA and a drug company can agree on the terms. Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research, says the FDA offered the option of restricted distribution for very severely affected patients in the case of Lotronex (alosetron). Lotronex was approved to treat irritable bowel syndrome in women, but caused ischemic colitis that could be fatal in some cases. After discussions, the manufacturer, GlaxoSmithKline, Research Triangle Park, N.C., decided to voluntarily withdraw the drug from the market in 2000. ■

—M.M.

(Continued from page 14)

to the labeling and sent letters out to doctors, but reports of long-term use of the drug continued.

When Other Risk Management Options Fail

The day you hear news about a drug coming off the market, it may appear to be a sudden, drastic step. But several other options to manage risks usually have been attempted before that point. The main risk management tools em-

ployed by the FDA are education through letters to health-care professionals (known within the FDA as "Dear Doctor" letters) and labeling changes, such as new warnings, sometimes boxed in black for emphasis. Also used are required Medication Guides, labeling specifically for patients that emphasizes significant risks and advises patients how to detect or avoid them. In some cases, a drug is labeled as "second line," meaning it is to be used only in patients for whom other treatments fail. In other

cases, a drug that is known to be dangerous is still made available under certain circumstances through what's known as restricted distribution (see box).

Sometimes these risk management techniques are effective, and other times they aren't. "We have our anecdotes, but there is little systematic study on the effect of drug labeling changes on physician behavior," says Temple.

Labeling changes were a partial success with the allergy drug Seldane. Studies showed use of Seldane with inappropriate drugs declined almost 90 percent, but that left considerable exposure to the dangerous combinations, some of which could be lethal.

The label of the heartburn treatment Propulsid (cisapride) was changed several times in 1998. The FDA cosponsored a study to evaluate the effect of various regulatory actions, and found that the percentage of patients inappropriately exposed to the drug was unchanged.

"We know that the farther out we are from the initial approval, the less likely we are to change behavior," Woodcock says. "Once a prescribing pattern has been established, it's hard to change it."

Clearly, the more special care that is required, the more physicians must remember, and the more we need other safeguards like spotting dangerous combination uses at the pharmacy level, the more of a challenge risk management becomes. "We do consider whether we are being unreasonable in our expectations, but sometimes that can't be known beforehand," Temple says.

Currently, the FDA is involved with several drug safety initiatives, including revamping the drug labeling for physicians to create a highlights section, a relatively short section that will describe the most critical information. Better education is a high priority. "We're looking into better ways to educate the public and doctors about changes in risk information, and to get information out faster," says Honig.

But FDA experts say the agency can't do it alone. The FDA judges drug risks for a population, doctors judge risks for individual patients, and patients judge the risks they'll take based on personal values. Ultimately, drug safety requires involvement of all parts of the health system. ■

Loosening

MORE THAN COUNTING CALORIES

By Linda Bren

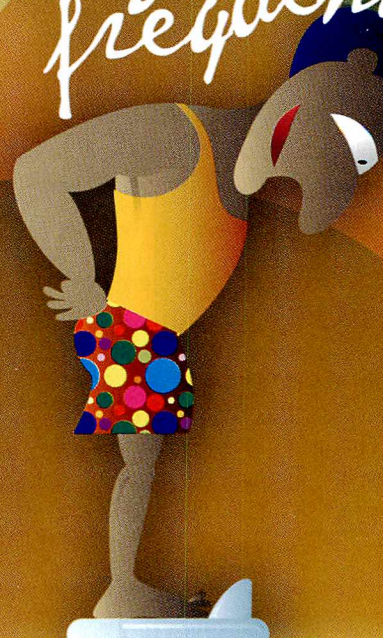
Americans are eating less fat, but getting fatter. We're putting on the pounds at an alarmingly rapid rate. And we're sacrificing our health for the sake of supersize portions, biggie drinks, and two-for-one value meals, obesity researchers say.

More than 60 percent of U.S. adults are either overweight or obese, according to the Centers for Disease Control and Prevention (CDC). While the number of overweight people has been slowly climbing since the 1980s, the number of obese people has nearly doubled since then.

No Laughing Matter

Excess weight and physical in-

weigh-in frequently



Weight:

activity account for more than 300,000 premature deaths each year in the United States, second only to deaths related to smoking, says the CDC. People who are overweight or obese are more likely to develop heart disease, stroke, high blood pressure, diabetes, gallbladder disease and joint pain caused by excess uric acid (gout). Excess weight can also cause interrupted breathing during sleep (sleep apnea) and wearing away of the joints (osteoarthritis).

Carrying extra weight means carrying an extra risk for cancer. "[Our] researchers have concluded that obesity increases the risk for many of the most common cancers worldwide, and perhaps cancer in general," says Melanie Polk, R.D., director of nutrition education at the

American Institute for Cancer Research (AICR), a nonprofit research and education organization in Washington, D.C.

In their review of more than 100 studies and international reports on obesity and cancer risk, completed in October 2001, researchers at the AICR concluded that obesity is consistently linked to post-menopausal breast cancer, colon cancer, endometrial cancer, prostate cancer, and kidney cancer.

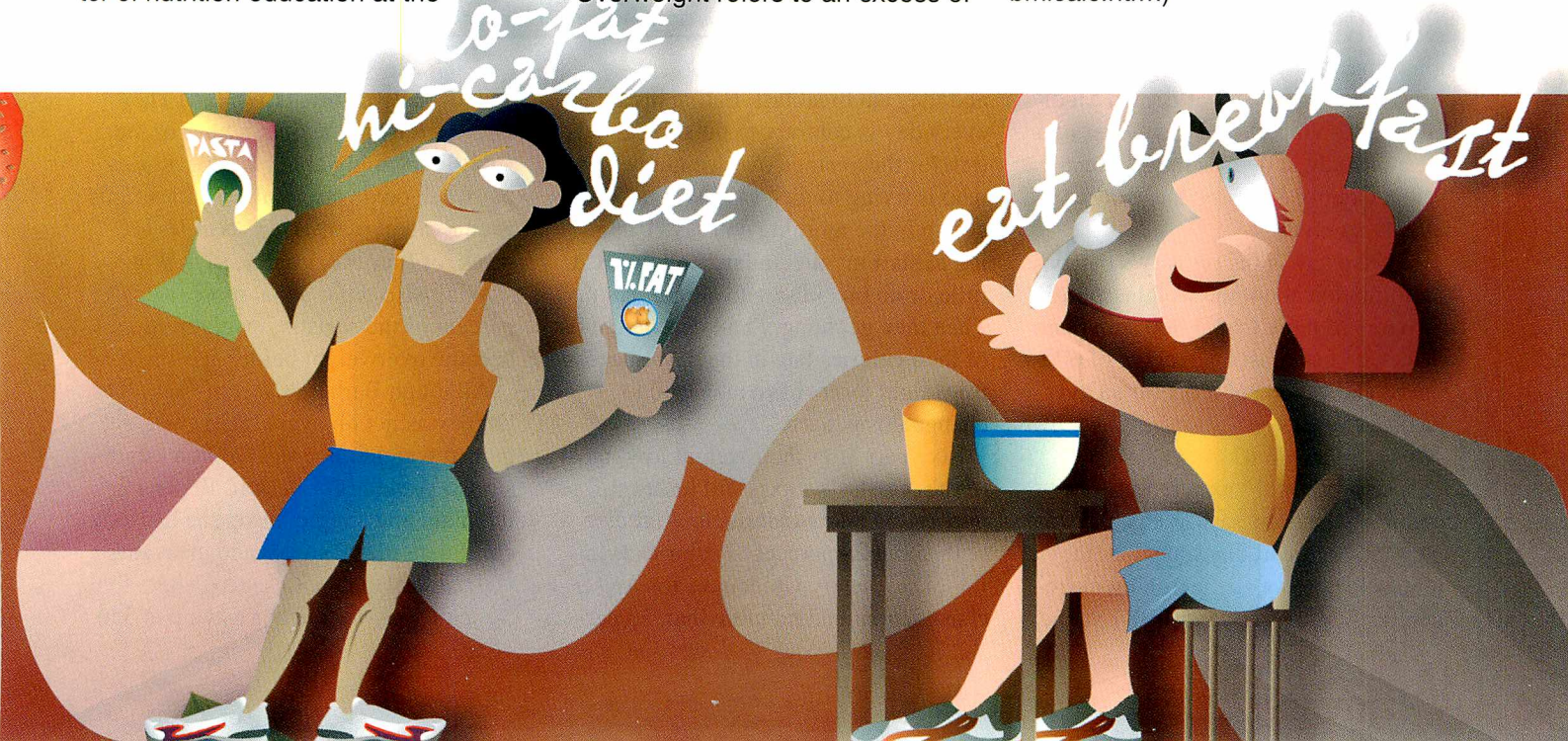
The public health epidemic of being overweight or obese in the United States has become so serious that Surgeon General David Satcher has prepared a national action plan to address the issue.

Are You Overweight?

Overweight refers to an excess of

body weight, but not necessarily body fat. Obesity means an excessively high proportion of body fat. Health professionals use a measurement called body mass index (BMI) to classify an adult's weight as healthy, overweight, or obese. (See the BMI chart, "Are You at a Healthy Weight?" on page 20.) BMI describes body weight relative to height and is strongly correlated with total body fat content in most adults.

BMI is determined by dividing a person's weight in kilograms by height in meters squared. To get your approximate BMI using pounds and inches, multiply your weight in pounds by 700, then divide the result by your height in inches, and divide that result by your height in inches a second time. (Or you can use the interactive BMI calculator at www.nhlbisupport.com/bmi/bmicalc.htm.)



A BMI of 18.5 to 24.9 is considered healthy, from 25 to 29.9 is overweight, and 30 or higher is obese. Generally, the higher a person's BMI, the greater the risk for health problems, according to the National Heart, Lung and Blood Institute (NHLBI). However, there are some exceptions. For example, very muscular people, like body builders, may have a BMI greater than 25 or even 30, but this reflects increased muscle rather than fat. "It is excess body fat that leads to the health problems such as type 2 diabetes, high blood pressure, and high cholesterol," says Eric Colman, M.D., of the Food and Drug Administration's division of metabolic and endocrine drug products.

In addition to a high BMI, having excess abdominal body fat is a health risk. Men with a waist of more than 40 inches around and women with a waist of 35 inches or more are at risk for health problems.

Obesity, once thought by many to be a moral failing, is now classified as a disease. The NHLBI calls it a complex chronic disease involving social, behavioral, cultural, physiological, metabolic, and genetic factors. Although experts may have different theories on how and why people become overweight, they generally agree that the key to losing weight is a simple message: Eat less and move more. Your body needs to burn more calories than you take in.

Successful 'Losers'

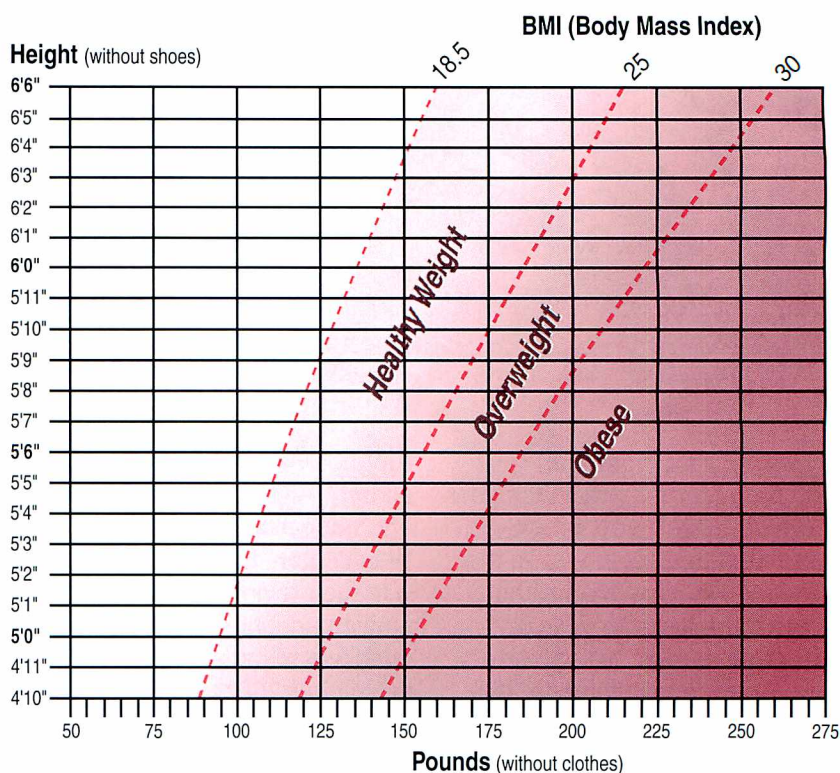
A popular weight-loss myth is that everyone who loses weight eventually gains it back, says Rena Wing, Ph.D., a professor of psychiatry at Brown Medical School. Wing, the co-developer of a research study known as the National Weight Control Registry, has worked to deflate this myth.

Tucked away in the registry's database is information about the weight-control behaviors of more than 3,000 American adults who have lost an average of 60 pounds and have kept it off for an average of six years.

How do they do it?

These successful losers report four common behaviors, says Wing. They eat a low-fat, high-carbohydrate diet, they monitor themselves by weighing in frequently, they are very physically active,

Are You at a Healthy Weight?



The BMI ranges shown above are for adults. They are not exact ranges of healthy and unhealthy weights. However, they show that health risk increases at higher levels of overweight and obesity. Even within the healthy BMI range, weight gains can carry health risks for adults.

Directions: Find your weight on the bottom of the graph. Go straight up from that point until you come to the line that matches your height. Then look to find your weight group.

- Healthy Weight: BMI from 18.5 up to 25 refers to healthy weight.
- Overweight: BMI from 25 up to 30 refers to overweight.
- Obese: BMI 30 or higher refers to obesity. Obese persons are also overweight.

Source: Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2000.

and they eat breakfast. Eating breakfast every day is contrary to the typical pattern for the average overweight person who is trying to diet, says Wing. "They get up in the morning and say 'I'm going to start my diet today,' and they eat little or no breakfast and a light lunch. Then they get hungry and consume most of their calories late in the day. Successful weight losers have managed to change this pattern."

Six years after their weight loss, most of the registry's successful losers still report eating a low-calorie, low-fat diet, with about 24 percent of calories from fat. (The Dietary Guidelines for Americans recommend no more than 30 per-

cent of daily calories from fat.) They also exercise for about an hour or more a day, expending about 2,800 calories per week on a variety of activities. This is equivalent to walking 28 miles a week, or four miles a day, says Wing.

Wing also reports that more than 70 percent of the registry's weight losers became overweight before age 18.

Although Barbara Croft of Columbus, Ohio, was not an overweight child, she gained weight once she left home and started cooking for herself. Replacing the plain and simple meals she had as a child with pizza, sodas, and meat and vegetables laden with sauces, the 5-foot-5-inch Croft worked her way up to 350

pounds. "I always ate from all the food groups—I just ate huge portions and I ate in between meals," says Croft.

When she was diagnosed with type 2 diabetes in February 1999, Croft got scared. "I worried about the health consequences—about going blind. I already have a little numbness in my feet."

Croft went on a diet and lost 200 pounds in 19 months. She has kept it off for a year and a half. "This is the third time I've lost over 100 pounds," says the 52-year-old, 150-pound Croft, "but this is the longest I've been able to keep the weight off." In her two previous weight losses, Croft ate nutritious meals, but didn't exercise. This time, she started walking for exercise, but could only walk about a block at first. "My husband went with me because he was afraid I wouldn't make it," she says. Now, Croft walks on a treadmill for 50 minutes a day—25 minutes each morning and night.

She still eats balanced meals, but restricts her portions. And she always eats breakfast. "I have Egg Beaters, two pieces of low-calorie bread, fruit, decaf coffee, and 8 ounces of water." Croft dines out almost every night, typically eating half her dinner of grilled chicken or salmon and a vegetable or salad. She sends the other half back, so she isn't tempted to overeat.

"Losing the weight was easy—maintaining it is much harder," says Croft.

Croft had tried commercial weight-loss programs in the past, but this last time she did it on her own. "You have to find out what works for you," she says. "If I eat butter or cheese, that seems to do me in. Beef is also a problem."

"It's hard to accept that I'm never going to be able to eat what I want," says Croft. But she knows the tradeoff is her health. Her diabetes is under control now without medication. And Croft says her knees don't hurt anymore, she can buy clothes in a regular store, and she started traveling again now that she can fit into an airplane seat.

Setting a Goal

The first step to weight loss is setting a realistic goal. By using the BMI chart on page 20 and consulting with your health-care provider, you can determine what is a healthy weight for you.



Barbara Croft maintains her 200-pound weight loss by preparing healthy meals, eating small portions, and exercising daily.

Studies show that you can improve your health with just a small amount of weight loss. "We know that physical activity in combination with reduced calorie consumption can lead to the 5 to 10 percent weight loss necessary to achieve remission of the obesity-associated complications," says William Dietz, M.D., Ph.D., director of the division of nutrition and physical activity at the CDC. "Even these moderate weight losses can improve blood pressure and help control diabetes and high cholesterol in obese or overweight adults."

To reach your goal safely, plan to lose weight gradually. The NHLBI recommends a weight loss of 1 to 2 pounds per week by decreasing the calories eaten or increasing the calories used by 500 to 1,000 calories per day. (Some people with serious health problems due to obesity may lose weight more rapidly under a doctor's supervision.) If you plan to lose more than 15 to 20 pounds, have any health problems, or take medication on a regular basis, a doctor should evaluate you before you begin a weight-loss program.

Changing Eating Habits

Dieting may conjure up visions of eating little but lettuce and sprouts—but you can enjoy all foods as part of a healthy diet as long as you don't overdo it on fat (especially saturated fat), sugars, salt and alcohol. To be successful at losing weight, you need to change your lifestyle—not just go on a diet, experts say.

Limit portion sizes, especially of foods high in calories, such as cookies, cakes, other sweets, french fries, and fats, oils, and spreads. Reducing dietary fat alone—without reducing calories—will not produce weight loss, according to the NHLBI's guidelines on treating overweight and obesity in adults.

Use the Food Guide Pyramid (page 22), developed jointly by the U.S. Department of Agriculture (USDA) and the Department of Health and Human Services, to help you choose a healthful assortment of foods that include vegetables, fruits, grains (especially whole grains), skim milk and fish, lean meat, poultry, or beans. Choose foods naturally high in fiber, such as fruits, vegetables, legumes (such as beans and lentils), and whole grains. The high fiber content of many of these foods may help you to feel full with fewer calories.

All calories are not created equal. Carbohydrate and protein have about 4 calories per gram, but fat has more than twice that amount (9 calories per gram). Just as for the general population, weight-conscious consumers should aim for a daily fat intake of no more than 30 percent of total calories.

Keep your intake of saturated fat at less than 10 percent of calories. Saturated fats increase the risk for heart disease by raising blood cholesterol. Foods high in saturated fats include high-fat dairy products (like cheese, whole milk, cream, butter, and regular ice cream), fatty fresh and processed meats, the skin and fat of poultry, lard, palm oil, and coconut oil.

If you drink alcoholic beverages, do so in moderation. Alcoholic beverages supply calories but few nutrients. A 12-ounce regular beer contains about 150 calories, a 5-ounce glass of wine about 100 calories, and 1.5 ounces of 80-proof distilled spirits about 100 calories.

Limit your use of beverages and

foods that are high in added sugars—those added to foods in processing or preparation, not the naturally occurring sugars in foods such as fruit or milk. Foods containing added sugars provide calories, but may have few vitamins and minerals. In the United States, the major sources of added sugars include non-diet soft drinks, sweets and candies, cakes and cookies, and fruit drinks and fruitades.

Using the Food Label

Under regulations from the FDA and the USDA, the food label, found on almost all processed foods, offers more complete, useful and accurate nutrition information than ever before. Even when restricting calories and portions, you can use the part of the food label called the Nutrition Facts panel to make sure you get all the essential nutrients for good health (see box, right).

You'll find the serving size and the number of servings per package listed at the top of the Nutrition Facts panel. The serving size affects all the nutrient amounts listed on the panel. For example, if there is one cup in a serving and the package contains two servings, you need to double the calories and other nutrient numbers if you eat the whole package. Many items sold as single portions—like a 20-ounce soft drink, a 3-ounce bag of chips, and a large bagel—actually provide two or more servings.

"If you zero in on the 'amount per serving' section of the Nutrition Facts panel, you can tell at a glance how many

How to Use the Nutrition Facts Label

Macaroni & Cheese

Start Here →

Limit these Nutrients

Get Enough of these Nutrients

Footnote

Nutrition Facts	
Serving Size 1 cup (228g) Serving Per Container 2	
Amount Per Serving	
Calories 250	Calories from Fat 110
% Daily Value*	
Total Fat 12g	18%
Saturated Fat 3g	15%
Cholesterol 30mg	10%
Sodium 470mg	20%
Total Carbohydrate 31g	10%
Dietary Fiber 0g	0%
Sugars 5g	
Protein 5g	
Vitamin A	4 %
Vitamin C	2 %
Calcium	20%
Iron	4 %

* Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Quick Guide to % DV

5% or less is Low

20% or more is High

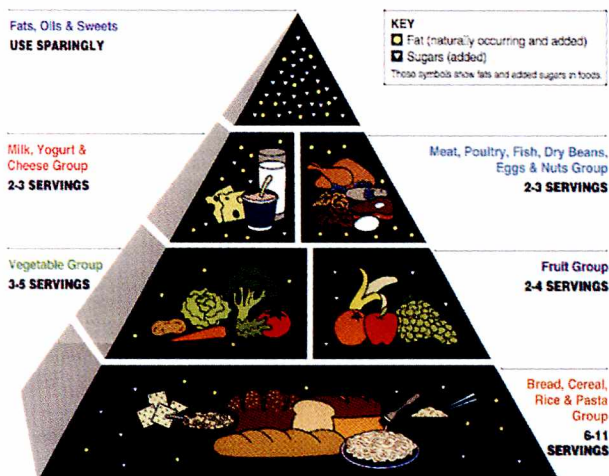
Use the **Nutrition Facts** Label not only to **limit** those nutrients you want to cut back on, but also to **increase** the ones you want to consume in greater amounts.

Look at the % Daily Value (%DV) column to see whether a food is high or low in nutrients. If you want to **limit** a nutrient (such as fat, saturated fat, cholesterol, sodium), choose foods with a lower %DV. To consume **more** of a nutrient (such as calcium, fiber, vitamins or minerals), choose foods with a higher %DV.

As a **quick guide**, foods with 5% DV or less contribute a small amount of that nutrient to your diet, while those with 20% DV or more contribute a large amount.

Remember, serving sizes are not recommended amounts, but are close to amounts people actually eat. They can help you compare similar foods.

Food Guide Pyramid



calories a serving has and whether a food is high in total fat, saturated fat, cholesterol, and sodium," says Naomi Kulakow, coordinator of food labeling education in the FDA's Center for Food Safety and Applied Nutrition. "These are items you should think about limiting in your diet."

The Nutrition Facts panel also shows how much dietary fiber, vitamin A, vitamin C, calcium, and iron are contained in a serving. These are nutrients you need for good health.

Also listed on the Nutrition Facts panel are the amounts of carbo-

hydrates, protein, and sugars contained in a serving. Use the panel to compare the amount of total sugars among similar products, and try to choose ones lower in sugars.

In addition to listing some nutrients by weight, the panel also gives this information as a percentage of Daily Value (%DV). The percentage of Daily Value shows how a serving of a food fits in with recommendations for a healthful diet and allows consumers to make comparisons between similar products.

For example, shoppers can use the %DV figures to find out which frozen

dinner is lower in saturated fat—particularly when it involves a comparative nutritional claim, such as reduced-fat.

“*You don’t need to know the precise definition of ‘low’ or ‘reduced,’*” says Kulakow. “Just look at the percentage of Daily Value and see which is higher or lower in the nutrient you are interested in.” Foods with 5 percent or less of the Daily Value are considered low in a nutrient, while those with 20 percent or more are high in the nutrient.

The percentages of Daily Value are based on a 2,000-calorie daily diet. But even if you eat less than 2,000 calories, the percentage of Daily Value can be used to determine whether a food is high or low in a particular nutrient.

“People use the food label too often to just restrict calories and fat—not to get enough nutrients,” says Kulakow. While restricting calories is important for weight loss, “most people have no idea how many calories they consume every day—especially if they eat out.” The percentage of Daily Value gives you a frame of reference and can be used to make dietary trade-offs, says Kulakow. “For example, if you eat a favorite food that’s high in fat at one meal, balance it with low-fat foods at other times of the day.”

Kulakow advises caution when choosing foods that are labeled “fat-free” and “low-fat.” Fat-free doesn’t mean calorie-free. To make a food tastier, sometimes extra sugars are added, which adds calories (see “Fat-Free vs. Regular Calorie Comparison,” right). So dieters should always check the Nutrition Facts panel to get complete information, says Kulakow.

For further guidance on using the Nutrition Facts panel, see www.cfsan.fda.gov/~dms/foodlab.html.

Increasing Physical Activity

Most health experts recommend a combination of a reduced-calorie diet and increased physical activity for weight loss. All adults should get at least 30 minutes of moderate physical activity on most, and preferably all, days of the week. But only 1 in 5 U.S. adults get the recommended amount of physical activity, according to a 1996 Surgeon General’s report.

In addition to helping to control

Fat-Free vs. Regular Calorie Comparison

You can lose weight by eating fewer calories and by increasing your physical activity. Reducing the amount of total fat and saturated fat that you eat is one way to limit your overall calorie intake. However, eating fat-free or reduced-fat foods isn’t always the answer to weight loss. This is especially true when you eat more of the reduced fat food than you would of the regular item. For example, if you eat twice as many fat-free cookies as you would regular cookies you actually have increased your overall calorie intake. The following list of foods and their reduced-fat varieties demonstrates that just because a product is fat-free, it doesn’t mean that it is “calorie-free.”



Fat-Free or Reduced-Fat		Regular	
	Calories		Calories
Reduced-fat peanut butter, 2 T	187	Regular peanut butter, 2 T	191
Reduced-fat chocolate chip cookies, 3 cookies (30 g)	118	Regular chocolate chip cookies, 3 cookies (30 g)	142
Fat-free fig cookies, 2 cookies (30 g)	102	Regular fig cookies, 2 cookies (30 g)	111
Nonfat vanilla frozen yogurt (<1% fat), ½ cup	100	Regular whole milk vanilla frozen yogurt (3-4% fat), ½ cup	104
Light vanilla ice cream (7% fat), ½ cup	111	Regular vanilla ice cream (11% fat), ½ cup	133
Fat-free caramel topping, 2 T	103	Caramel topping, homemade with butter, 2 T	103
Low-fat granola cereal, approx. ½ cup (55 g)	213	Regular granola cereal, approx. ½ cup (55 g)	257
Low-fat blueberry muffin, 1 small (2½ inch)	131	Regular blueberry muffin, 1 small (2½ inch)	138
Baked tortilla chips, 1 oz.	113	Regular tortilla chips, 1 oz.	143
Low-fat cereal bar, 1 bar (1.3 oz.)	130	Regular cereal bar, 1 bar (1.3 oz.)	140

Infographic by Renée Gordon

Source: National Heart, Lung and Blood Institute.
Nutrient data taken from Nutrient Data System for Research,
Nutrition Coordinating Center, University of Minnesota.

Avoid 'Fad' Diets

The cabbage soup diet, the low-carbohydrate and high-protein diet, and other so-called "fad" diets are fundamentally different from federal nutrition dietary guidelines and are not recommended for losing weight.

Fad diets usually overemphasize one particular food or type of food, contradicting the guidelines for good nutrition, which recommend eating a variety of foods. These diets may work at first because they cut calories, but they rarely have a permanent effect.

A high-protein diet is one fad diet that has remained popular over the years. "High-protein items may also be high in fat," says Robert Eckel, M.D., professor of medicine at the University of Colorado Health Sciences Center in Denver. High-fat diets can raise blood cholesterol levels, which increases a person's risk for heart disease and certain cancers.

High-protein diets force the kidneys to try to get rid of the excess waste products of protein and fat, called ketones. A buildup of ketones in the blood (called ketosis) can cause the body to produce high levels of uric acid, which is a risk factor for gout (a painful swelling of the joints) and kidney stones. Ketosis can be especially risky for people with diabetes because it can speed the progression of diabetic renal disease, says Eckel.

"It's important for the public to understand that no scientific evidence supports the claim that high-protein diets enable people to maintain their initial weight loss," says Eckel. "In general, quick weight-loss diets don't work for most people." ■

—L.B.



weight, physical activity decreases the risk of dying from coronary heart disease and reduces the risk of developing diabetes, hypertension, and colon cancer. Researchers also have found that daily physical activity may help a person lose weight by partially lessening the slow-down in metabolism that occurs during weight loss.

Exercise does not have to be strenuous. Moving any part of your body, regardless of how fast or slow, is considered physical activity. And studies show that short sessions of exercise several times a day are just as effective at burning calories and improving health as one long session.

To lose weight and to maintain a healthy weight after weight loss, many adults will likely need to do more than 30 minutes of moderate physical activity daily.

Prescription Weight-Loss Drugs

For obese people who have difficulty losing weight through diet and exercise alone, there are a number of FDA-approved prescription drugs that may help. "On average, individuals who use weight-loss drugs lose about 5 percent to 10 percent of their original weight, though some will lose less and some more," says the FDA's Colman.

Tips for Eating Out

- Choose foods that are steamed, garden fresh, broiled, baked, roasted, poached or stir-fried.
- Share food, such as a main dish or dessert, with your dining partner.
- Take part of the food home with you, and refrigerate immediately. You may want to ask for a take-home container when the meal arrives. Spoon half the meal into it, so you're more likely to eat only what's left on your plate.
- Request your meal to be served without gravy, sauces, butter or margarine.
- Ask for salad dressing on the side, and use only small amounts of full-fat dressings. ■

—L.B.



Steam your veggies



Take food home

All of the prescription weight-loss drugs work by suppressing the appetite *except for* Xenical (orlistat). Approved by the FDA in 1999, Xenical is the first in a new class of anti-obesity drugs known as lipase inhibitors. Lipase is the enzyme that breaks down dietary fat for use by the body. Xenical interferes with lipase function, decreasing dietary fat absorption by 30 percent. Since undigested fats are not absorbed, there is less calorie intake, which may help in controlling weight. The main side effects of Xenical are cramping, diarrhea, flatulence, intestinal discomfort, and leakage of oily stool.

Meridia (sibutramine), approved by the FDA in 1997, increases the levels of certain brain chemicals that help reduce appetite. Because it may increase blood pressure and heart rate, Meridia should not be used by people with uncontrolled high blood pressure, a history of heart disease, congestive heart failure, irregular heartbeat, or stroke. Other common side effects of Meridia include headache, dry mouth, constipation and insomnia.

Other anti-obesity prescription drugs that were approved by the FDA many years ago based on short-term, limited data include: Bontril (phendimetrazine tartrate), Desoxyn (methamphetamine) and Ionamin and Adipex-P (phentermine). These drugs are only to be taken for a few weeks.

"There is no magic pill for obesity," says David Orloff, M.D., director of the FDA's division of metabolic and endocrine drug products. "The best effect you're going to get is with a concerted long-term regimen of diet and exercise. If you choose to take a drug along with this effort, it may provide additional help."

Until September 1997, two other drugs, fenfluramine (Pondimin and others) and dexfenfluramine (Redux), were available for treating obesity. But at the FDA's request, the manufacturers of these drugs voluntarily withdrew them from the market after newer findings suggested that they were the likely cause of heart valve problems. The FDA recommended that people taking the drugs stop and that they contact their doctor to discuss their treatment. (For the latest information on this topic, visit www.fda.gov/cder/news/feninfo.htm.)

For More Information

Weight-control Information Network (WIN)

National Institute of Diabetes and Digestive and Kidney Diseases
1-877-946-4627
www.niddk.nih.gov/health/nutrit/win.htm

American Dietetic Association

1-800-877-1600, or 800-366-1655 for recorded food/nutrition messages
www.eatright.org

Prescription weight-loss drugs are approved only for those with a BMI of 30 and above, or 27 and above if they have other risk factors, such as high blood pressure or diabetes.

Beware of Unproven Claims

Some dietary supplement makers claim their products work for weight loss. These products are not reviewed by the FDA before they are marketed. "Under our existing laws, manufacturers have the responsibility for ensuring that their dietary supplement products are safe and effective," says Christine Lewis Taylor, Ph.D., R.D., director of the FDA's office of nutritional products, labeling, and dietary supplements.

Many weight-loss products claim to be "natural" or "herbal," but this does not necessarily mean that they're safe. These ingredients may interact with drugs or may be dangerous for people with certain medical conditions. If you are unsure about a product's claims or the safety of any weight-loss product, check with your doctor before using it.

Over-the-Counter Drugs

Over-the-counter (OTC) weight-control drugs contain the active ingredient

American Obesity Association

1-800-98-OBESE (1-800-986-2373)
www.obesity.org

National Weight Control Registry

1-800-606-NWCR (1-800-606-6927)
www.nwcr.ws

This study gathers information from people who have successfully lost weight and kept it off. The registry would like to hear from anyone 18 or older who has lost at least 30 pounds and maintained that weight loss for at least a year.

phenylpropanolamine, which is also used as a nasal decongestant. The FDA recently asked drug manufacturers to discontinue marketing products containing phenylpropanolamine, based on evidence linking the substance to an increased risk of hemorrhagic stroke (bleeding in the brain). In addition, the FDA issued a public health advisory in November 2000, warning consumers to stop using products containing this ingredient.

The FDA is proposing to classify phenylpropanolamine as "not generally recognized as safe," and is proceeding with regulatory actions that will likely remove this ingredient from the market.

Worth the Effort

"Losing weight requires major lifestyle changes, including diet and nutrition, exercise, behavior modification, and—when appropriate—intervention with drug therapy," says Judith S. Stern, Sc.D., professor of nutrition and internal medicine at the University of California, Davis, and vice president of the American Obesity Association. "But it is always worth making the effort to improve your health." ■

DIABETES

A Growing Public Health Concern

By Carol Lewis



Either you have it or you don't.

That's the message that the American Diabetes Association (ADA) is driving home to millions of people who believe they may be "borderline diabetic," or that their "sugar is just a bit high." Convenient phrases and stereotypes such as these don't adequately describe one of the nation's leading causes of death and disability. In fact, they tend to only minimize problems associated with the disease. The bottom line? An accurate diagnosis is essential, because while a person can live a long and healthy life with diabetes, ignoring it or not taking it seriously can be deadly.

"It's crucial to know when you have *diabetes*, to hear the diagnosis, and to pay attention to it," says ADA president Christopher D. Saudek, M.D.

Saudek, who also heads up the diabetes center at Johns Hopkins University School of Medicine in Baltimore, says he's seen people deny their diabetes "almost to the point of death."

Diabetes mellitus is a chronic disease in which the pancreas produces too little or no insulin, impairing the body's ability to turn sugar into usable energy. Doctors often use the full name "diabetes mellitus," rather than "diabetes" alone,

to distinguish this disorder from diabetes insipidus—a different disease altogether that is characterized by excess urination, but is unrelated to blood sugar.

The number of people diagnosed with diabetes has increased more than sixfold from 1.6 million in 1958 to 10 million in 1997, according to the Centers for Disease Control and Prevention (CDC) in Atlanta. Today, some 16 million people have the disease—making it a leading cause of death in the United States—yet 5 million don't know they have it. And nearly 800,000 new cases of diabetes are diagnosed each year.

There is no cure for the disease, and the resulting health complications from poorly controlled diabetes are what make it so frightening. Consistently high blood sugar levels can, over time, lead to blindness, kidney failure, heart disease, limb amputations, and nerve damage. In fact, diabetes is the leading cause of new cases of blindness in adults between the ages of 20 and 74, and it accounts for 40 percent of people who have kidney failure. Cardiovascular disease is 2 to 4 times more common among people with diabetes, and is the leading cause of diabetes-related deaths. The risk of stroke is also 2 to 4 times higher in people with diabetes, and 60 percent to 65 percent have high blood pressure.

Despite these numbers, Saudek says diabetes can be very well-managed and that people can expect to live full and productive lives. Much of the treatment, however, depends largely on self-care practices. It's important, Saudek says, not only to target good behaviors, but also to consistently follow through with them.

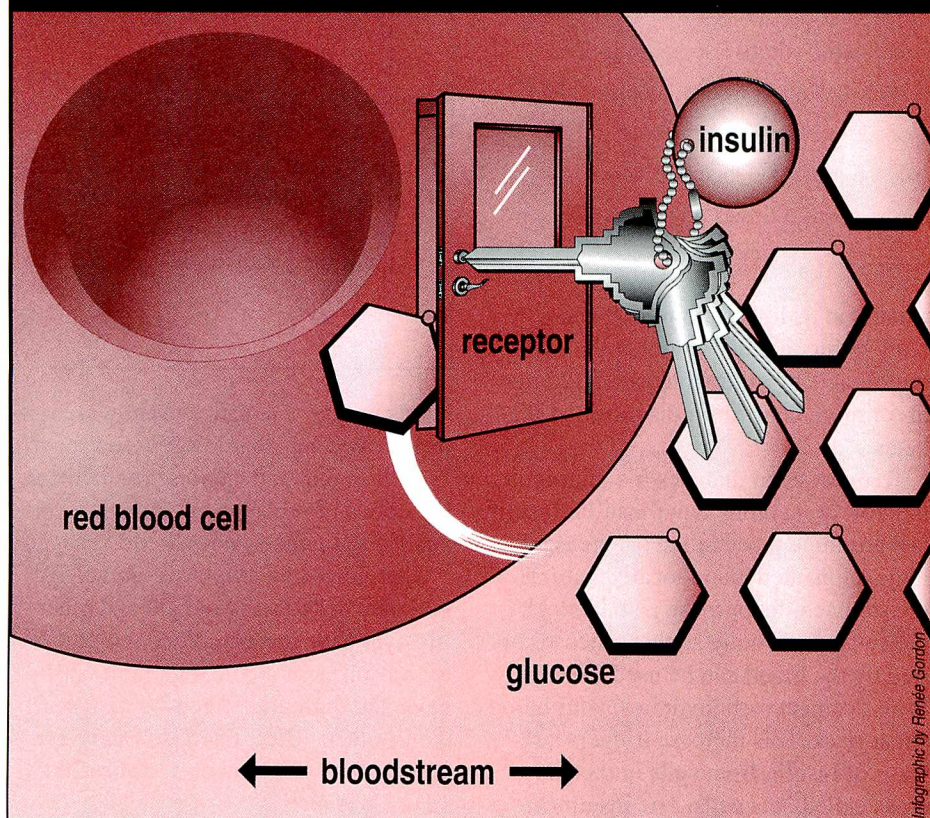
Monitoring blood sugar levels is a key component in treatment and management of the disease. Research has indicated that people who keep their blood sugar levels within individual target ranges set by their doctors stand a good chance of reducing the risk of complications from diabetes. Moreover, in many cases intensive lifestyle changes in diet and exercise actually can prevent, reduce or delay the risk of developing one type of the disease.

Understanding Diabetes

Blood sugar, or blood glucose, refers to the amount of sugar in the blood. The brain's only food is glucose; therefore, blood sugar must be maintained at a certain level for the brain to function normally. After eating any meal that contains carbohydrate or protein, a person's blood sugar normally rises, often to between 120 and 130 milligrams per deciliter (mg/dL), but generally not above 140 mg/dL. Every day, every hour, blood sugar levels vary, even in people who don't have diabetes.

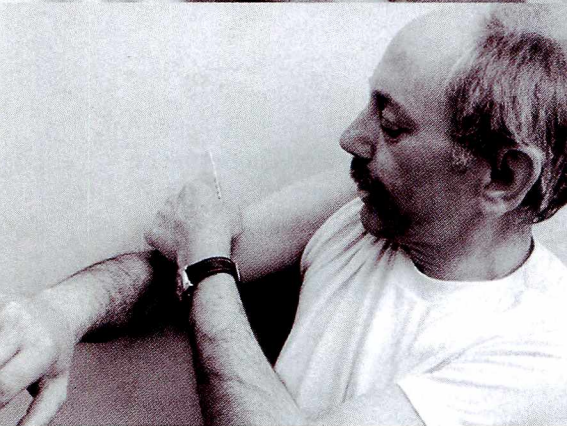
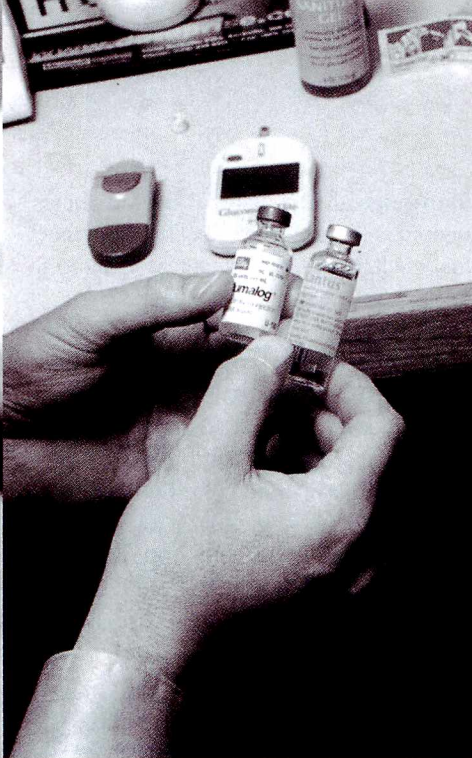
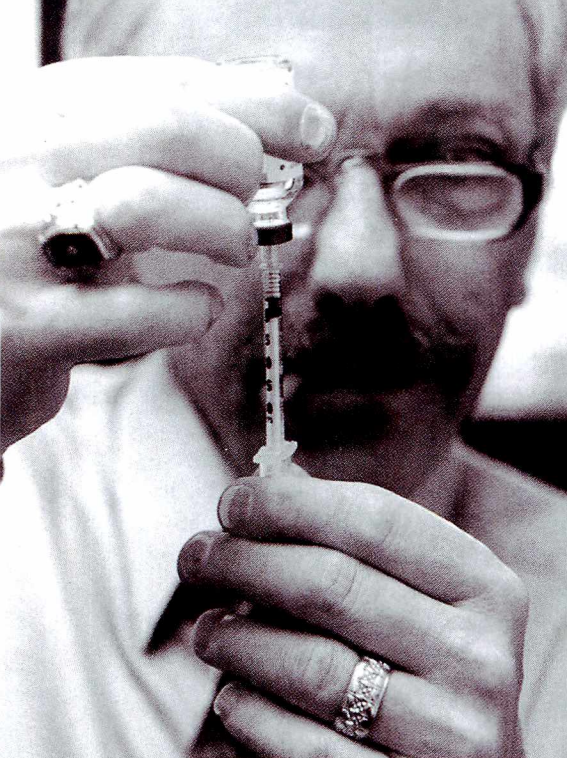
If the blood sugar level drops too low

The Role of Insulin



Carbohydrates that we eat make our blood glucose (sugar) rise. To utilize the carbohydrates and lower the blood sugar, insulin opens the doors of the body's cells to glucose circulating in the blood. The glucose enters the cells and is used as the cells' fuel for energy. Insulin binds to a spot on the cell surface called a receptor. Likened to a lock and key, insulin is the key that opens up the lock (receptor) so that glucose can pass through the door into the cell. Using this analogy in type 1 diabetes, the keys have been stolen (no insulin is made by the pancreas). In type 2, the door won't open fully even with the right key (insulin resistance).

Source: Christopher D. Saudek, Richard R. Rubin, and Cynthia S. Shump. *The Johns Hopkins Guide to Diabetes*. Baltimore: The Johns Hopkins University Press, 1997.



Paul Keister, whose life depends on daily injections of insulin, monitors his blood sugar levels using a blood glucose meter. He then injects the insulin needed based on the reading.

(hypoglycemia), a person's ability to reason can become impaired. When the blood sugar levels are too high (hyperglycemia), diabetes is diagnosed. Often the diagnosis is obvious to doctors because symptoms such as thirst, fatigue, weight loss, frequent urination, and persistent vaginal infections in women are evident. In the presence of these symptoms, diabetes can be confirmed by a random test of blood sugar, meaning that the blood is drawn at any time during the day, rather than specifically before eating breakfast. If the person is thirsty and urinating large amounts, the blood sugar usually will be well over 200 mg/dL, sometimes up in the 300s and 400s, or higher.

But when the classic symptoms are not present, the criteria for diagnosing diabetes include a fasting blood glucose test. This means that the blood glucose is drawn at least 10 hours following a meal early in the morning, when it is

usually at its lowest point in the day. A random blood glucose higher than 200 mg/dL and a fasting glucose of 125 mg/dL or more confirms a diagnosis of diabetes.

To understand diabetes it's important to know something about insulin. Insulin is a hormone made in the pancreas, a large, elongated gland located behind the stomach. Its purpose is to "unlock" the cells of the body so that glucose carried by the blood can be used for energy. When you eat carbohydrates, your blood sugar rises. This increase triggers a release of insulin from cells in the pancreas called beta cells. The insulin "opens the doors" of the cells throughout the body to glucose. As glucose enters the cells, the blood sugar level falls back to normal—and the release of insulin ebbs until the next time protein or carbohydrates are eaten.

The basic problem in type 1 diabetes is that the pancreas quits making insulin. In type 2, it either doesn't make enough or something interferes with the action of the insulin that is made. Someone with type 1 diabetes must inject replacement insulin to stay alive. Blood sugar

Characteristics of Type 1 Diabetes

- Age of onset under 40 years old, most common in children; some older people develop this type
- Thin to normal body weight
- Quick onset with thirst, frequent urination, and weight loss symptoms developing and worsening over days to weeks
- Usually no known family history, but in rare cases there can be
- No major risk factors; risk is increased if strong family history exists
- Usually more than one shot daily of insulin treatment always needed to control diabetes
- Difficult to keep fluctuating blood sugar in ideal range
- Blood sugar is sensitive to small changes in diet, exercise, and insulin dose
- Can be caused by a combination of heredity and exposure to some factor during life that triggers autoimmune destruction of the insulin-producing beta cells in the pancreas ■

—C.L.

levels in type 2 diabetes usually are controlled by drugs that lower blood sugar as well as diet and exercise. Sometimes, injections of replacement insulin are needed to maintain normal blood sugars.

The increasing emphasis on the importance of reducing weight and other lifestyle changes, combined with the latest advances in medical therapies, all have had dramatic effects on diabetes control (see "Diet, Exercise Delay Type 2 Diabetes," September–October 2001 *FDA Consumer*).

While it is fairly easy to diagnose, determining what type of diabetes a person has can be both challenging and critical. An accurate diagnosis matters because there are different ways to treat the different types of diabetes in order to stave off potential long-term complications.

Type 1 Diabetes

People with type 1 diabetes, such as 56-year-old Paul Keister of Arlington, Va., must inject replacement insulin to control the levels of glucose in their

blood. Frequent tests (several times a day) using blood obtained from finger **pricks** are required to maintain good blood sugar control.

In type 1 diabetes, the beta cells of the pancreas are destroyed by the body's immune system, which is responsible for recognizing and destroying outside invaders such as viruses or bacteria.

In a process that is not well-understood, the body begins to think that its own pancreatic beta cells are "foreign" and sets off an "autoimmune" response that ends up destroying the cells. As a result, no insulin can be produced.

Type 1 diabetes accounts for 5 percent to 10 percent of all people with the disease. This type is sometimes called juvenile diabetes because it most commonly appears initially in children or adolescents. However, people older than 30 also may develop the condition.

Scientists believe that some environmental factor—possibly a viral infection or something related to nutrition—causes the immune system to destroy the insulin-producing cells. At 30 years old, Keister was diagnosed with type 1 diabetes following a stomach illness and after a stubborn tooth infection refused to go away.

The resulting insulin deficiency is usually severe. Without injections of enough insulin to control increases in the blood sugar, diabetic ketoacidosis (coma and potentially death) can result. Today, type 1 diabetes is treatable, and ketoacidosis preventable by taking sufficient amounts of insulin and by following dietary guidelines set by doctors and the ADA.

Type 2 Diabetes

Type 2 diabetes accounts for more than 90 percent of cases in the United States. In this type, the pancreas continues to produce insulin; however, the body develops resistance to its effects, resulting in a different kind of insulin deficiency than in type 1. Although the blood sugar rises in type 2 diabetes for different reasons than in type 1, the symptoms and potential complications are similar.

Certain racial and ethnic groups, including blacks, American Indians, Mexican-Americans and other Hispanics, are at increased risk for getting the disease.



Once Dale Driscoll determines his blood sugar level, he carefully measures the ingredients needed to consume a low-calorie, low-fat meal in line with his physician's recommendations.

In many cases, intensive lifestyle changes in diet and exercise actually can prevent, reduce or delay the risk of developing one type of the disease.

And obesity is a risk factor for type 2 diabetes. Although doctors don't know exactly why, they say it's clear that the muscle cells (where most of the sugar breakdown occurs) of obese people are far less responsive to insulin than are muscle cells of thinner people. An obese person's pancreas has to put out large amounts of insulin to keep blood sugars normal. The likelihood of developing type 2 diabetes in people who are at risk increases with age and weight gain.

The typical person with type 2 diabetes is older, overweight, and often has a family history of diabetes. Dale Driscoll of Frederick, Md., was diagnosed with type 2 diabetes at about the same age that Paul Keister was diagnosed with type 1—an indication that age alone is not a reliable diagnostic criterion. And there is little evidence to suggest that diabetes runs in Driscoll's family.

It's important, says Saudek, to know that some people don't fit neatly into ei-

ther of these diagnostic "boxes." Like Driscoll, none of Keister's relatives on either parent's side has ever had diabetes, even though type 1 occurs in people with a genetic susceptibility. There are exceptions to the general rule that diabetes occurring in the young is type 1, and that diabetes occurring in older people is type 2. Likewise, taking insulin does not mean you have type 1 diabetes, just as obesity is not a sure diagnostic sign of type 2.

Type 2 diabetes is nearing epidemic proportions in the United States, according to diabetes experts, due to an increased number of older Americans and a greater prevalence of obesity and sedentary lifestyles.

Gestational Diabetes

Between 3 percent and 5 percent of pregnant women in the United States develop gestational diabetes—elevated blood sugar due to certain hormones that

Characteristics of Type 2 Diabetes

- Age of onset over 40 years old, most common in adults; some younger people develop this type
- Overweight; occasionally occurs in people of normal weight
- Usually slow onset with thirst, frequent urination, and weight loss symptoms developing over weeks to months, or even years
- Can be “silent disease”
- Usually runs in families
- Treatment usually begins with diet and exercise, progressing to pills and later to insulin
- Easier to control without fluctuating blood sugar range
- Blood sugar may respond to weight loss, and/or change in diet and exercise; blood sugar may be less responsive to small changes in insulin dose
- Can be caused by combination of heredity, insulin resistance, and deficiency of the insulin-producing beta cells of the pancreas ■

—C.L.

An accurate diagnosis matters because there are different ways to treat the different types of diabetes in order to stave off potential long-term complications.

Advances At A Glance

- **GlucoWatch:** Glucose monitoring device worn like a watch; detects blood glucose levels through the skin; must be calibrated to a glucose meter; approved March 2001. Cygnus Inc., Redwood City, Calif.
- **Sof-Tact:** Semi-automated home blood glucose monitor that uses light suction vacuum to hold skin in place while integrated apparatus lances skin. Device automatically transfers small amount of blood to a biosensor strip, and blood glucose test result is delivered in 20 seconds. Eliminates need for traditional finger-stick method; can be used on forearm or upper arm; approved November 2000. Abbott Laboratories, Abbott Park, Ill.
- **Continuous Glucose Monitoring System:** Continuous measure of tissue glucose levels in adults with diabetes. Records levels at five-minute intervals for up to three days; information is then downloaded on computer for review by health-care practitioner; must be used in conjunction with finger-stick tests; approved June 1999. MiniMed Inc., Sylmar, Calif.
- **Lasette:** Portable, battery-operated laser; means for drawing blood without using traditional lancets (small, razor-sharp devices for puncturing skin); for adults and children; approved December 1998. Cell Robotics International Inc., Albuquerque, N.M.
- **Q-103 Needle Management System:** Used to remove certain hypodermic needles from insulin syringes and store them safely for later disposal; device holds up to 5000 removed needles; approved December 2000. QCare International LLC, Marietta, Ga.
- **Apligraf:** Wound dressing that helps heal diabetic foot ulcers, open foot sores that can lead to amputation; approved June 2000. Organogenesis Inc., Canton, Mass.
- **Dermagraft:** Skin substitute used to help in the wound closure of diabetic foot ulcers; helps replace and rebuild damaged tissue in diabetic foot ulcers; approved September 2001. Advanced Tissue Sciences, La Jolla, Calif.
- **Other devices:** Over 100 glucose meters and several external insulin pumps approved in the last several years.

occurs only during pregnancy. It is important to diagnose and treat gestational diabetes properly because it increases the risk of a baby growing larger than he or she would have been, and a large baby may have difficulty during *delivery*, or may be born by cesarean section. Keeping blood sugar within a normal range during the pregnancy reduces these risks. Women who experience gestational diabetes have a greater risk of developing diabetes later in life. One large study found that more than half of women who had gestational diabetes eventually developed type 2 diabetes.

Controlling Diabetes—Treatment Goals

Daily monitoring and careful control of blood sugar levels are the most important steps that people with diabetes can take, says David G. Orloff, M.D., director of the FDA's division of metabolic and endocrine drugs. Over the past decade, “tight control” of blood sugar with a goal of achieving and maintaining near-normal levels has become the standard of care for both type 1 and type 2 diabetes. Maintaining normal levels is difficult, Orloff says, “but good glyce-mic control is key to preventing long-term complications.” Another reason for good blood sugar control, Orloff adds, “is that it does make a difference in how people feel.”

Joanna K. Zawadzki, M.D., of the FDA's metabolic and endocrine drugs division, cautions that “just having a blood glucose monitor is not adequate follow-up to your diabetic treatment.” People need better blood sugar control than just enough to avoid symptoms, she says. Keeping blood sugars always between 150 mg/dL and 200 mg/dL, for instance, may help a person avoid obvious symptoms, but may not be good enough to avoid the long-term complications. “Diabetes treatment is a complex approach that comprises a team of professionals, the patient, his or her family, and treatment and goals agreed upon by the team.” Zawadzki adds, “Work with your doctor to come up with reasonable expectations for your individual treatment plan.”

People with type 1 diabetes need insulin from the time they are initially diagnosed, throughout life. Type 2 diabetes may often mean a prescribed regimen of

Insulin Preparations

Since 1982, most of the newly approved insulin preparations have been produced by inserting portions of DNA (“recombinant DNA”) into special lab-cultivated bacteria or yeast. This process allows the bacteria or yeast cells to produce complete human insulin. Recombinant human insulin has, for the most part, replaced animal-derived insulin, such as pork and beef insulin. More recently, insulin products called “insulin analogs”

have been produced so that the structure differs slightly from human insulin (by one or two amino acids) to change onset and peak of action. The following table lists some of the more common insulin preparations available today. Onset, peak, and duration of action are approximate for each insulin product, as there may be variability depending on each individual, the injection site, and the individual’s exercise program.

Type of Insulin	Examples	Onset of Action	Peak of Action	Duration of Action
Rapid-acting	Humalog (lispro) Eli Lilly	15 minutes	30-90 minutes	3-5 hours
	NovoLog (aspart) Novo Nordisk	15 minutes	40-50 minutes	3-5 hours
Short-acting (Regular)	Humulin R Eli Lilly Novolin R Novo Nordisk	30-60 minutes	50-120 minutes	5-8 hours
Intermediate-acting (NPH)	Humulin N Eli Lilly Novolin N Novo Nordisk	1-3 hours	8 hours	20 hours
	Humulin L Eli Lilly Novolin L Novo Nordisk	1-2.5 hours	7-15 hours	18-24 hours
Intermediate- and short-acting mixtures	Humulin 50/50 Humulin 70/30 Humalog Mix 75/25 Humalog Mix 50/50 Eli Lilly Novolin 70/30 Novolog Mix 70/30 Novo Nordisk	The onset, peak, and duration of action of these mixtures would reflect a composite of the intermediate and short- or rapid-acting components, with one peak of action.		
Long-acting	Ultralente Eli Lilly	4-8 hours	8-12 hours	36 hours
	Lantus (glargine) Aventis	1 hour	none	24 hours

diet and exercise in the initial phases of the disease. Frequently, however, and certainly over time, changes in diet and exercise aren’t enough to keep blood sugar at near-normal levels. The next step for these people is taking a medicine that lowers the blood sugar. There are two basic kinds: insulin therapy and oral medications.

Insulin Replacement Therapy

Before the availability of insulin, treatments for people with type 1 diabe-

tes were unpleasant and often ineffective. A low-carbohydrate, semi-starvation diet and exercise were all doctors had to offer. People lost more and more weight, and many of them died within the first year of diagnosis. Like many scientific advances, the discovery of replacement insulin in the 1920s was nothing short of a miracle.

Insulin lowers blood sugar by both increasing the removal of glucose from the blood and reducing the production of glucose by the liver. In type 1 diabetes,

since there is virtually no insulin produced by the pancreas, people need insulin all the time—more at mealtimes to “cover” the carbohydrates and protein eaten, and less during other times to maintain as even a level as possible. In people with type 2 diabetes, insulin injections sometimes are needed to supplement the amount produced by the pancreas.

Insulin injections are given under the skin (subcutaneously) into the fat layer, usually in the arm, thigh, or abdomen.

Oral Antidiabetes Medications

Category	Action	Generic Name	Brand Name	Manufacturer	Approval Date	Comments
Sulfonylurea	Stimulates beta cells to release more insulin	Chlorpropamide	Diabinese	Pfizer	10/58	Generally <i>taken one to two</i> times daily, before meals; can have interactions with other drugs. First generation sulfonylurea (older drug)
		Glipizide	Glucotrol	Pfizer	5/84	Second generation used in smaller doses than first generation
		Glyburide	DiaBeta/ Micronase/ Glynase	Aventis, Pharmacia and Upjohn	5/84	
		Glimepiride	Amaryl	Aventis	11/95	
Meglitinide	Works with similar action to sulfonylureas	Repaglinide	Prandin	Novo Nordisk	12/97	Taken before each of three meals
Nateglinide	Works with similar action to sulfonylureas	Nateglinide	Starlix	Novartis	12/00	Taken before each of three meals
Biguanide	Sensitizes the body to the insulin already present	Metformin	Glucophage	Bristol Myers Squibb	3/95	Taken two times daily with food for best results
		Metformin (long lasting)	Glucophage XR	Bristol Myers Squibb	10/00	
		Metformin with glyburide	Glucovance	Bristol Myers Squibb	7/00	
Thiazolidinedione (Glitazone)	Helps insulin work better in muscle and fat; lowers insulin resistance	Rosiglitazone	Avandia	SmithKline Beecham (now GlaxoSmithKline)	5/99	Taken once or twice daily with food; very rare but serious effect on liver
		Pioglitazone	Actos	Takeda Pharmaceuticals	7/99	
Alpha-Glucose Inhibitor	Slows or blocks the breakdown of starches and certain sugars; action slows the rise in blood sugar levels following a meal	Acarbose	Precose	Bayer	9/95	Should be taken with first bite of meal
		Miglitol	Glyset	Pharmacia and Upjohn	12/96	

Insulin cannot be given by mouth because it is destroyed by digestive enzymes in the stomach. Small syringes with very thin needles make the injections nearly painless. In recent years, several external insulin pumps, which deliver insulin continuously through a thin, flexible tube placed under the skin, have been developed.

There are more than 20 types of insulin available in four basic forms, each with a different time of onset and duration of action (see “Insulin Preparations,” page 31). The decision as to which insulin to choose is based on an individual’s lifestyle, a physician’s pref-

erence and experience, and the person’s blood sugar levels. Among the criteria considered in choosing insulin are: how soon it starts working (onset), when it works the hardest (peak time), and how long it lasts in the body (duration).

Oral Medications

Pills to treat diabetes—antidiabetic agents—are used only in type 2 treatment. Four general classes of drugs work in different ways to lower blood sugar (see “Oral Antidiabetes Medications,” above). There are some risks associated with the use of these drugs. For example, sulfonylureas, which stimulate the beta

cells in the pancreas to release more insulin, can be associated with severe low blood sugar levels, particularly when the person has other medical problems or is taking other medications. And in order for them to work, a person’s pancreas must be making at least some insulin. That is why oral medications will not work for the treatment of type 1 diabetes.

For best results, oral medications must be taken regularly every day, not irregularly or started and stopped according to blood sugar. Since many dosages are available, a physician can change the dosage if blood sugars are running too high or too low. Many of these drugs can

be used in combination with one another, but any change in their use should be done only at the direction of a *health-care professional*.

Driscoll's doctor found that oral medications were not effective in controlling his blood sugar, and he replaced them with insulin injections. In retrospect, Driscoll says, "while the pills were easier to deal with, insulin has made the greatest difference in my life." In addition, Driscoll has shed 40 of the 100 pounds recommended by his doctor as part of his treatment plan.

Organ Transplants

Pancreas transplants and kidney transplants are options for people with type 1 diabetes, if they have kidney failure (about one-third of type 1 patients). Since the 1970s, doctors have performed pancreas transplants along with kidney transplants in hopes of halting or reversing the complications of diabetes. The procedure has met with some success. Kidneys alone are transplanted to replace kidneys that have totally failed. Pancreas transplants may be done simultaneously or after kidney transplants, to try to "cure" diabetes. But pancreases are often not transplanted unless a kidney is also needed, says Saudek, "because the surgery is so major and the need for continuous immune suppression is more dangerous than taking insulin." Saudek adds that unavailability of transplantable kidneys and pancreases also is a factor.

A kidney transplant for people with type 1 and type 2 diabetes can restore the body's ability to perform a number of crucial functions, including filtering wastes from the blood and controlling the body's fluid and chemical balance. Receiving a new pancreas at the same time may actually improve kidney survival. In addition, a new pancreas can improve blood sugar levels to normal, or close to it.

Organ transplants aren't always successful. Besides the risk inherent in any major surgery, the body can reject the new organ days or even years after the transplant. Because of this, transplant recipients will likely need to take immunosuppressive drugs the rest of their lives. The drugs themselves carry significant health risks, such as cancer, but

they work to prevent the immune system from rejecting the new organ.

Another noteworthy therapeutic intervention, and one that Keister hopes to be considered for, is a procedure called islet cell transplantation. Researchers have known for some time that transplanting these insulin-producing cells may provide a possible cure for type 1 diabetes. The process to date is still not perfected, but there is some evidence that researchers may be getting closer to their goal.

"From the biologics perspective," says Philip Noguchi, M.D., director of the FDA's division of cellular and gene therapy, "emphasis on products for diabetes is clearly experimental at this time, but potentially very promising." In islet cell transplantation, doctors extract islet cells from the pancreas of a person who has recently died and then infuse them via a catheter into the liver of the person with diabetes. The liver instead of the pancreas is the location for the transplant because it is easier and less invasive to access the large vein in the liver than a pancreatic vein, and islet cells that grow in the liver closely mimic normal insulin secretion.

Because the cells are very fragile, the procedure is fraught with problems. One of the biggest obstacles is the availability of fresh islet cells. There is a shortage of organ donors in the United States, and the supply of islet cells, like kidneys and pancreases, is limited. Another challenge is the ability to isolate the cells. It takes several donor pancreases to isolate enough islet cells for a single transplant.

Still, "when it comes to trying new treatments," says Keister, "I'm going to push the envelope." Since his diabetes was detected prior to glucose meters, Keister says the greatest contribution he can give back to society is his "participation in new trials using the latest technology to learn more about the effects of treatment on the disease."

While additional studies are underway to learn more about the long-term effects of islet cell transplantation, Noguchi says, "at the moment there are a number of well-established procedures for type 1 and type 2 diabetes that let people live normal lives."

Prognosis

Saudek says it's a scientific fact that

For More Information

American Diabetes Association

Attn: Customer Service
1701 N. Beauregard St.
Alexandria, VA 22311
1-800-DIABETES (1-800-342-2383)
To contact your local affiliate, call
1-888-DIABETES (1-888-342-2383)
www.diabetes.org

National Center for Chronic Disease Prevention and Health Promotion

Centers for Disease Control and Prevention (CDC)
Division of Diabetes Translation
P.O. Box 8728
Silver Spring, MD 20910
1-877-CDC-DIAB (1-877-232-3422)
www.cdc.gov/diabetes

Juvenile Diabetes Foundation International

120 Wall Street
New York, NY 10005
1-800-533-CURE (1-800-533-2873)
www.jdfcure.org

National Institute of Diabetes and Digestive and Kidney Diseases

National Diabetes Information Clearinghouse
1 Information Way
Bethesda, MD 20892
1-800-860-8747
www.niddk.nih.gov/health/diabetes/diabetes.htm

the outlook for people with diabetes can be excellent if the disease is well taken care of. Several major studies, including the Diabetes Control and Complications Trial Research Group, in which people with type 1 diabetes have been followed for years, compared the effects of standard and more intensive diabetes treatments on the development and progression of long-term complications. The more intensive treatments prevented or slowed diabetes complications.

So, says Saudek, "It's doable. Taking advantage of what's available puts people in the best possible position to be strong and healthy when diabetes is ultimately cured." ■



By John Henkel

Bioterrorism Page Opens Door to Information

As part of a heightened awareness of bioterrorism threats that began in October with the discovery of anthrax-tainted letters, the FDA has created a special Web site that links to background about bioterrorism and offers a quick study on the subject. The page, at www.fda.gov/oc/opacom/hottopics/bioterrorism.html, links to FDA information on use of anthrax drugs by pregnant women, treating potential outbreaks, and the safety of the food supply. Links to information from other government sources such as the Centers for Disease Control and Prevention, the National Library of Medicine, and the Department of Defense also can be found at the site. For example, you can learn what to do if you find a suspicious letter, what the differences are between anthrax and the flu, and if you should buy anthrax-treating antibiotics such as Cipro through online vendors. If you still have questions, the page also has a special section with questions and answers on food contamination, vaccines, and various other bioterrorism topics.

Curbing Risky Student Behavior

Half of all U.S. high school students have had sexual intercourse. About 17 percent of all high school students carried a weapon in the last month. Nearly 19 percent of high school students seriously considered suicide in the last year. Seventy percent of all high school students have tried smoking at least once.

These sobering facts from the Centers for Disease Control and Prevention (CDC) underscore the importance of programs aimed at reducing potentially dangerous behavior among children of high school age. The CDC, through its Adolescent and School Health program, has created a Web site to further understanding of what's being done to cut down on these risky teen activities.

At www.cdc.gov/nccdphp/dash/, the site reviews the Youth Risk Behavior Surveillance System, which gleans teen behavior data through periodic studies of students nationwide who describe their behaviors candidly in questionnaires. One section of the site compares statistics from all studies dating back to 1991 and offers a free CD-ROM with data from 1999, the most recent year in which study data have been compiled and analyzed. Also on the site is an overview of how school health programs are effectively shaping the health and social well-being of teen-age students.



Resisting Antibiotic Resistance

Disease-causing microbes that have become resistant to drug therapy are an increasing public health problem. Many diseases—tuberculosis, gonorrhea, and childhood ear infections, for example—have become difficult to treat with antibiotic drugs. In fact, about 70 percent of bacteria that cause infections in hospitals are resistant to at least one of the drugs most commonly used to treat infections. This is because bacteria and other infection-causing organisms can develop ways to survive drugs meant to kill or weaken them. This condition, called antibiotic resistance, is the subject of an FDA Web site that offers information from the FDA and other sources.

At www.fda.gov/oc/opacom/hottopics/anti_resist.html, the site helps explain antibiotic resistance with a pair of informative articles from *FDA Consumer* magazine, a list of tips for preventing the problem, fact sheets, and frequently asked questions. Health professionals and industry users will find materials such as the conclusions of an FDA task force that reviewed the problem, as well as a government-wide public health plan that examines factors such as antibiotic resistance control, research, and product development. The site also links to pages that describe a national system for monitoring the antibiotic resistance problem.

Get Involved—Volunteer!

Interested in giving something back to your community? Do you have a special skill that you could lend to help others? If so, dozens of opportunities are available through volunteer programs run by federal agencies and private organizations. The Department of Housing and Urban Development has created a gateway site that makes it easy to examine many of these programs. Whether your skills are in reading instruction, science education, the outdoors, or working with kids or seniors, there's an activity you can assist with. Helpers are needed for jobs such as monitoring water quality, land management, and leading tours of park areas. The HUD site also links to volunteer positions in organizations such as the American Cancer Society, the American Red Cross, and Habitat for Humanity (which builds homes for needy folks). Interested? Check out the opportunities at www.hud.gov/volunteering/index.cfm#Federal.



Foreign Drug Firm Pleads Guilty To Felony Charges

By Carol Lewis

A French pharmaceutical company has been fined \$33 million for deliberately failing to disclose to Food and Drug Administration officials all of the locations where the antibiotic cefaclor was being manufactured. The monetary penalty is one of the largest ever imposed in a criminal pharmaceutical prosecution.

Paris-based Roussel Uclaf S.A. was ordered to pay the fine after pleading guilty on behalf of its Italian subsidiary company, Biochimica Opos S.p.A., to felony charges of conspiracy and introducing adulterated drugs into interstate commerce with the intent to defraud or mislead. Cefaclor, approved to treat various infections, was being marketed to American consumers, but was manufactured outside the United States at facilities not disclosed to the FDA. The purpose of the illegal scheme was to increase sales of cefaclor in the United States, according to FDA special agents.

U.S. District Judge Peter J. Messitte in Greenbelt, Md., handed down the fine in October 2001. The case represents the first time that a foreign corporation has been criminally punished for defrauding the FDA concerning an approved drug product manufactured outside the United States and marketed to the American public.

Roussel Uclaf manufactured and distributed various drug products in the United States. Biochimica Opos, an Italian subsidiary, developed, manufactured, promoted, and sold generic drug products, including cefaclor. Personnel from Roussel Uclaf had certain oversight responsibilities for the business activities of both companies.

According to the FDA's office of criminal investigations (OCI), the case began in May 1996, when the agency conducted a post-approval inspection of Biochimica Opos regarding production of cefaclor.

"Post-approval inspections are performed once a manufacturer is authorized to market a drug," says Kim Rice, an OCI assistant special agent in charge.

"They allow the FDA to monitor and evaluate the integrity of the drug and the process used to produce it." Discrepancies in manufacturing procedures were found during the inspection, leading investigators to become suspicious about the production of cefaclor. For example, the inspection team noted inconsistencies in statements made to them about information they had requested.

Pharmaceutical manufacturers that legally export drugs to the United States are required to create and maintain production and control records for each batch of a drug product. These records include the identity of each active and inactive ingredient used, the location of the manufacturing facility, laboratory test results, a description of each step in the drug's manufacturing process, and the names of all persons performing and supervising each significant step in the drug's manufacture.

In this case, employees provided batch production records at the May 1996 inspection that misrepresented the production method for cefaclor, and falsely showed the manufacturing facilities involved in the production of the drug. In addition, some of the essential ingredients used to manufacture cefaclor were obtained from unapproved sources, and false records, including raw material log books, a double software application, and work orders, were kept to conceal the fraudulent activities.

In October 1996, after the inspection, Roussel Uclaf admitted to various violations in connection with the production of cefaclor at the Opos facility, including failure of the company to make the antibiotic according to the original drug application approved by the FDA.

Roussel officials also admitted to similar violations in the manufacturing processes for two other approved antibiotics, clindamycin and minocycline. They confirmed that critical manufacturing steps were being secretly performed at other locations. Roussel then recalled



the three drugs from pharmaceutical manufacturers in the United States, and withdrew each drug's approved marketing application. Opos also stopped shipping the drugs to the United States at this time.

In early 1997, the FDA inspected yet another Italian drug manufacturer suspected of being involved with Opos' violations. In fact, evidence proved that the Italian company was obtaining essential ingredients for making cefaclor from unapproved sources. Once more related events surfaced, the FDA's Center for Drug Evaluation and Research referred the case to the OCI's special prosecution staff.

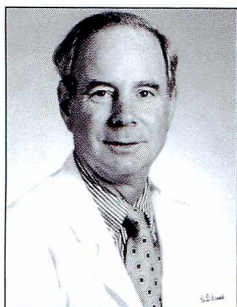
"This case was a very difficult one to develop due to the fact that the illegal acts occurred outside the U.S.," says Rice. "Most of the documents of evidentiary value," he says, "were located in foreign countries." In addition, Rice adds that the documents were written primarily in French, Italian or German, and that some potential witnesses were foreign citizens "who may not have been subject to U.S. subpoena power."

OCI's investigation revealed that Roussel misled the FDA by not disclosing that unapproved facilities in Italy, France and Romania were involved in the manufacture of cefaclor. Rice says that foreign authorities helped OCI criminal investigators obtain documents and conduct interviews with many witnesses. ■



A 'Touch' Of Diabetes?

By Christopher D. Saudek, M.D.



Sometimes, inside the health-care professions and health-care regulatory agencies, we hear the opinion that type 2 diabetes isn't that big a deal. It isn't cancer and it isn't AIDS. It's just a lifestyle disease. People shouldn't have let themselves get overweight. There are lots of pills available, and then there's always insulin. It is amazing how often physicians don't

even bother to tell people that they have diabetes; they soften the message with euphemisms like, "We'll have to watch your sugar," or the oldest of all, "You only have a touch of diabetes."

Statistics do not support this casual attitude. Available through the American Diabetes Association's Web site, www.diabetes.org, the numbers are sobering: 15.7 million people have diabetes in the United States, and about 5.4 million don't even know it. Over 200,000 people will die of diabetes this year. About 15 percent of diagnosed people already have long-term complications when they are first told they have diabetes, and the mean time between onset and diagnosis is estimated to be seven years. Type 2 diabetes is the leading cause of end-stage renal disease, preventable amputations, working-age blindness, and a major cause of heart disease and stroke. It cost over \$98 billion in the United States in 1997. The stats go on, and paint an ugly picture of inadequate treatment with devastating results.

But isn't diabetes easily treated? Isn't it a disease people can easily take care of, if they would only pay attention? "Easily" is a huge misconception. It may be easy to say, "Diet and exercise, give up on the sweets, check your numbers, know your blood pressure and cholesterol and stop smoking, have your eyes checked, your feet, your lipids and your A1c. Oh yes, and keep losing the weight." But have you, the reader, ever tried to take such good care of your health? Probably only if you have diabetes.

Adding things up, people with diabetes are expected to think about their disease perhaps 20 to 30 times a day, between worrying every time they eat, exercise, check their blood sugar or take a medication.

As new medications and new technologies are developed, it is worth thinking about what they mean for the person with diabetes. The new is too often dismissed by a summary comment: "Too expensive;" "a convenience item;" "too complicated for the average patient;" "not proven to be better." These put-downs were probably used when disposable syringes replaced boiling glass syringes, when ultrafine needles replaced thick needles. (I talked with a person the other day who had

found the pan her deceased mother used to boil her glass syringe). Better drugs, better meters, insulin pens and pumps translate into better self-care and fewer complications. And "too complicated" almost never applies: very little is too complicated for the average patient, and they need all the help they can get.

What about too complicated for the health-care professional? Those of us specializing in diabetes may be able to keep the medication options and the monitoring guidelines reasonably straight in our minds. But when diabetes is only a small part of a person's professional practice, it does present a huge challenge. In my opinion, the best thing to come along in the treatment of diabetes is the Certified Diabetes Educator, or CDE. It is a whole profession of people trained and certified in helping people with diabetes take care of themselves. People with diabetes and physicians who care for them should take advantage of the CDE.

So if diabetes is so complicated, so difficult to manage for the patient and health-care professional alike, is there any point trying? The evidence all points to a resounding "Yes." Large, definitive clinical trials such as the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study have proven conclusively that not only do blood glucose control and control of other risk factors matter, but they are achievable.

I believe, therefore, that it is up to us in the health-care professions and the health segment of the government to keep pushing the medications and the technologies forward. A safe, reliable pill to help people lose weight, regardless of whether it independently affects blood glucose, would have an enormous effect in controlling diabetes, since obesity-related insulin resistance is the major underlying cause of type 2 diabetes. Thousands of people with diabetes will benefit from any new medication that some people will respond well to, that has fewer side effects, or that will keep some people off insulin for a while longer. Dramatic advances like continuous or non-invasive blood glucose monitoring will come gradually and incrementally.

It must always be remembered that the cost of diabetes is in the complications and in the personal toll it takes. The incremental expense of new drugs and new technologies makes up a relatively small part of the total cost of diabetes. We therefore have to continue the progress in making safe, effective drugs and devices available until treatment is as easy as taking an aspirin a day. ■

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