ADHD
Not Just for Kids Anymore
Avoid Deep Vein Thrombosis: Keep the Blood Flowing
Experts give advice to help prevent blood clots in the legs.

Merck Withdraws Vioxx; FDA Issues Public Health Advisory
Citing concerns about heightened cardiovascular risk, the maker of the popular arthritis drug Vioxx has voluntarily withdrawn the product from the market.

Flu Prevention 2004–2005: An Update
A look at vaccine recommendations for this flu season.

ADHD: Not Just for Kids Anymore
Several drugs have been approved to help treat the symptoms of ADHD in adults.

The Importance of Public Comment to the FDA
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Facing Infertility
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Inside Cover: Color-enhanced photograph taken through a microscope of sperm fertilizing a human egg. For information on infertility and its treatments, see page 24.
Attention-deficit hyperactivity disorder (ADHD) is one of the most publicized and recognized childhood developmental problems. Research published in a psychiatric journal in 2000 indicates that between 3 percent and 5 percent of all U.S. children are affected by the inattention, hyperactivity, and impulsiveness that characterize the condition.

What is less well-known is that studies have found that between 30 percent and 70 percent of those who had ADHD as children still have symptoms as adults. Few adults, however, are identified or treated for the condition.

Diagnosing an adult with ADHD is difficult, according to the National Institute of Mental Health (NIMH). Adults usually don’t know that they have the condition. Oftentimes, they find it difficult, if not impossible, to manage routine tasks such as getting to work on time, getting dressed, and paying their bills.

Some adults with ADHD find out they have it when their child is diagnosed with the disorder. The symptoms of distractibility, impulsivity, and restlessness seen in their child are similar to what they’ve experienced for years. Others may be told they have ADHD when they seek professional help for depression, anxiety, or other emotional problems, according to the NIMH.

For more on adults with ADHD, see our cover story titled “ADHD: Not Just for Kids Anymore,” beginning on page 14.

Happy Holidays from the Staff of FDA Consumer.

Raymond Formanek Jr.
Editor

**Observations**

**New Drug for Neuropathic Pain**

People with diabetes who experience the pain associated with nerve damage (diabetic peripheral neuropathy) have a new treatment option—the first FDA-approved drug for managing the burning, tingling, and numbness sensations in the feet, legs, or hands that mark this condition.

The drug, Cymbalta (duloxetine), was approved in September 2004 for treating the condition, the most common complication of diabetes.

In clinical trials, people treated with Cymbalta reported less pain compared to those given an inactive substance (placebo). Fifty-eight percent of people treated with Cymbalta reported at least a 30 percent sustained reduction of pain. In comparison, 34 percent of people treated with a placebo reported sustained pain reduction. The most commonly reported side effects were nausea, dry mouth, constipation, and diarrhea. In some cases, patients experienced dizziness and hot flashes.

Cymbalta is manufactured by Eli Lilly and Company of Indianapolis.

**New Lab Test to Screen Infants**

Newborns can be screened for a variety of infant diseases using a new test done on blood from heel-stick samples—the same type of sample used for state-mandated newborn screening tests. The blood sample is measured for levels of amino acids and substances called free carnitine and acylcarnitines. The test, NeoGram Amino Acids and Acylcarnitines Tandem Mass Spectrometry Kit, provides screening information that, when used with clinical evaluation...
and other tools, can determine a newborn baby's risk for disorders related to metabolism of these substances.

While small amounts of these substances are found in everyone, abnormally high amounts, or abnormal patterns, may indicate different disease states called inborn errors of metabolism. These diseases include phenylketonuria (PKU), maple syrup urine disease (MSUD), medium chain Acyl-CoA dehydrogenase deficiency (MCAD), isovaleric acidemia, homocystinuria, and hereditary tyrosinemia.

These diseases can cause developmental delay, seizures, mental retardation, and death. With early identification, many of the effects of these diseases can be significantly reduced, with improved outcomes and improved quality of life.

PerkinElmer Life and Analytical Sciences Inc. of Norton, Ohio, manufactures the screening test.

Rx Depot to Stop Importing Drugs From Canada

The FDA has announced the filing of a consent decree of permanent injunctive action against Rx Depot Inc. and Rx of Canada LLC, based on violations of the Federal Food, Drug, and Cosmetic Act. Both firms and corporate officers Carl Moore and David Peoples admitted liability for causing the importation of unapproved drugs from Canada, and they agreed to stop.

"The defendants' illegal importation of drugs posed a significant public health threat," says Dr. Lester M. Crawford, Acting FDA Commissioner. This applies to unapproved drugs that are imported back into the United States and U.S.-manufactured drugs that are imported back into the United States by parties other than the manufacturer. Because these drugs are not subject to FDA oversight and are not continuously under the custody of a U.S. manufacturer or authorized distributor, their quality is unpredictable. They could be outdated, contaminated, or counterfeit, or could contain the wrong amount of the active ingredient. The drugs may also have been held under uncertain storage conditions.

The consent decree permanently restrains the defendants from any illegal importation of prescription drugs. The decree gives the FDA inspection authority to ensure compliance and sets a penalty of $4,000 per day for any violation.

Drugs for Radiation Contamination

Two drugs that have been used for decades as investigational treatments in emergencies were approved by the FDA in August 2004 to treat radiation contamination due to plutonium, americium, or curium. Pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) help eliminate these radioactive materials from the body, lowering the risk of developing certain cancers and other biological effects. The drugs are the first approved to treat contamination by the three radioactive substances.

To encourage submission of new drug applications for the two drugs, the FDA announced in September 2003 the specific conditions and findings under which the products could be approved.

Radioactive materials could be released from laboratory or industrial accidents or through terrorist attacks using a radiation dispersal device, commonly called a "dirty bomb." Contamination could occur through a variety of routes, including ingestion, inhalation, or direct contact through wounds. Ca-DTPA and Zn-DTPA are usually administered into the bloodstream, but for people whose contamination is only by inhalation, the drugs can be given by nebulized inhalation.

These products should not be administered at the same time. Ca-DTPA is more effective than Zn-DTPA during the first 24 hours after contamination. So if both products are available, Ca-DTPA should be given as the first dose. If additional treatment is needed, treatment should be switched to Zn-DTPA. After the initial 24 hours, Zn-DTPA and Ca-DTPA are similarly effective.

The main side effect of Ca-DTPA is the loss of certain essential metals such as zinc, which can be replaced by taking oral zinc supplements.

Ca-DTPA and Zn-DTPA are manufactured by Hameln Pharmaceuticals of Hameln, Germany.
New drug combinations to attack HIV, the virus that causes AIDS, and an injectable product to correct facial fat loss have been added to the list of approved treatments for people with HIV.

The FDA has approved two fixed-dose combination treatments for HIV-1 infection: Epzicom and Truvada. The control of HIV and AIDS generally requires simultaneous use of three or more drugs from different drug classes. Combination products bring together different HIV and AIDS drugs in a single medication or co-package to help make treatment regimens less complicated for people to follow.

“Simplifying treatment regimens by reducing the number of pills and times per day patients need to take them provides significant public health benefits,” says Dr. Lester M. Crawford, Acting FDA Commissioner.

Epzicom and Truvada are indicated for use in combination with other antiretroviral drug products from different classes for the treatment of adults with HIV-1 infection. Antiretroviral drugs attack HIV, which is a retrovirus, by interfering with the virus's ability to use specific enzymes that it needs to survive.

Epzicom is a fixed-dose combination of two antiretroviral drugs that are approved individually under the brand names Ziagen (abacavir sulfate) and Epivir (lamivudine). Truvada is a fixed-dose combination of two antiretroviral drugs that are approved individually under the brand names Viread (tenofovir disoproxil fumarate) and Emtriva (emtricitabine).

The FDA completed its review of Epzicom, a product of GlaxoSmithKline, in 10 months and its review of Truvada, a product of Gilead Sciences, in four months.

Sculptra, an injectable filler to correct facial fat loss in people infected with HIV, was recently approved under an expedited agency review. Sculptra is the first such treatment approved for a condition known as lipoatrophy, or facial wasting, a sinking of the cheeks, eyes, and temples caused by the loss of fat tissue under the skin.

Sculptra was shown to produce significant increases in skin thickness, adding volume to facial tissue and restoring shape in areas of the face with fat loss. After an initial treatment series, repeat treatments may be needed to maintain the correction. Studies reported an improvement in the quality of life among those treated and less of the anxiety and depression often associated with lipoatrophy.

Sculptra is an injectable form of poly-L-lactic acid, a biodegradable, biocompatible synthetic polymer from the family of alpha hydroxy acids that has been widely used for many years in dissolvable stitches, bone screws, and facial implants.

In studies, patients were given three to six injections of Sculptra at two-week intervals and were followed for two years. The studies showed that the product was safe and that it significantly improved facial appearance. Most side effects were related to the injection itself, and included nodules, redness, swelling, and bruising in the injection area.

Sculptra should be used only in people with HIV by health care providers who are fully familiar with the entire product package insert and product training materials provided by the drug maker, Dermik Laboratories of Berwyn, Pa. The FDA has not approved the use of the product for other indications, such as to treat wrinkles.

It is estimated that 900,000 to 1 million people in the United States are HIV-positive, although about one-third are not diagnosed. Some 50 percent will develop lipoatrophy. An estimated 150,000 to 350,000 people could potentially benefit from the new filler.

New Device to Treat Severe Deformities

The FDA has approved a device for children who have thoracic insufficiency syndrome, a term used to describe severe deformities of the chest, spine, and ribs that prevent normal breathing and lung development.

The Vertical Expandable Prosthetic Titanium Rib, an implanted device, was approved in September 2004 under the humanitarian device exemption (HDE), which makes medical devices available on a limited basis for patients with rare medical conditions. The device is a curved metal rod that is attached to ribs near the spine using hooks located at both ends of the device. It is intended to help straighten the spine and separate ribs so that the lungs can grow and fill with enough air to breathe. The device is lengthened or replaced as the patient grows, requiring repeat operations every six months.

An HDE is a special regulatory marketing approval for medical devices that treat conditions affecting fewer than 4,000 people annually in the United States.

The new device, manufactured by Synthes Spine Co. of West Chester, Pa., is not intended to correct conditions other than chest wall instability. It should not be used in children younger than 6 months, girls older than 14, or boys over 16.
A Safer Food Supply

Federal and state agencies have announced a new collaboration to protect the nation's food supply from contamination. The U.S. Department of Agriculture, the FDA, and the Department of Homeland Security signed an agreement with the National Association of State Departments of Agriculture in September 2004. This agreement will improve federal-state response plans for food and agricultural emergencies.

For the first phase of the project, a group of federal, state, and local officials will gather information about how food and agricultural safety should be handled within the various states. During the second phase, the group will develop an interagency response plan and conduct exercises to test and refine it. Phase three, which will conclude by June 2005, involves developing guidelines on how federal agencies will assist local response and recovery efforts.

For more information about food security, visit the FDA’s Web page at www.cfsan.fda.gov/~dms/fsterr.html.

Implanted Lens Corrects Nearsightedness

A plastic lens that is permanently implanted into the eye to correct moderate to severe nearsightedness has been approved by the FDA.

The lens, called the Artisan, is implanted in front of the eye's natural lens. It is intended for use in healthy eyes in people with stable vision.

Manufactured by Ophtec USA Inc. of Boca Raton, Fla., the Artisan is intended to reduce or eliminate nearsightedness in adults, and it will offer people another alternative to glasses, contact lenses, and laser surgery such as LASIK. However, the Artisan may not eliminate the need for glasses because it does not correct astigmatism. Glasses may need to be worn for night driving or other activities performed in low light. They may also be needed for reading.

Ophtec studied the use of the Artisan in the United States in 662 patients with moderate to severe nearsightedness. After three years, 92 percent had 20/40 or better vision—considered standard vision necessary to obtain a driver’s license—and 44 percent had 20/20 or better.

One potential concern raised by the study was the loss of endothelial cells in the corneas of patients who received the implants. The endothelium is a layer of cells that lines the undersurface of the cornea and is essential to keeping the cornea clear. The three-year study data showed a continual steady loss of endothelial cells of 1.8 percent a year. It is not known whether this loss will continue at the same rate, or what the long-term effect of this device on the cornea's health might be. To minimize any potential long-term effects, the FDA is requiring the labeling for the new lens to specify that it should be used only on people whose corneal endothelial cells are dense enough to withstand some loss over time.

Other adverse events reported in the study by less than 1 percent of patients included retinal detachment, cataract development, and corneal swelling.

Draft Plan for Flu Pandemic

Health and Human Services Secretary Tommy G. Thompson has released a draft Pandemic Influenza Response and Preparedness Plan. A flu pandemic is a global event in which a new strain of flu virus circulates and infects large numbers of people. Unlike the gradual changes that occur in the influenza viruses that infect people each flu season, a pandemic influenza virus represents a major, sudden change in the virus' structure.

Flu pandemics are rare; three occurred during the 20th century. In 1968, the Hong Kong flu outbreak resulted in nearly 34,000 deaths. In 1957, the Asian flu pandemic killed about 70,000. And in 1918, the Spanish flu pandemic caused 20 million to 50 million deaths worldwide.

A pandemic could occur if strains of bird (avian) flu were to combine with the flu virus that affects humans. This could create a new strain that could spread easily among humans. There have been several different bird flu viruses identified in poultry in recent years. One of these viruses killed birds and some people in Asia. Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam were affected by widespread flu outbreaks in poultry in early 2004. More than 100 million birds either died from the disease or were killed to contain the outbreaks. Human cases were reported only in Thailand and Vietnam. In the United States, there have been outbreaks of avian flu in poultry, one human case, and no reports of human deaths, according to the Centers for Disease Control and Prevention (CDC). The CDC and the World Health Organization continue to monitor avian flu activity.

Released in August 2004, the HHS plan aims to protect against pandemic influenza in five key areas: surveillance, vaccine development and production, antiviral stockpiling, research, and public health preparedness. The National Institute of Allergy and Infectious Diseases recently announced two projects that support development and production of investigational vaccines against strains of avian influenza.

To view the draft plan on pandemic influenza online, visit www.hhs.gov/inv/pandemicplan.
Animal Drugs for Limited Uses, Minor Species

An animal drug measure signed into law in August 2004 will help make more medications legally available to veterinarians and animal owners to treat minor animal species. The new law also will encourage the availability of treatments for uncommon diseases in the major animal species.

The major animal species are cattle, horses, swine, chickens, turkeys, dogs, and cats. Minor species are all other animals, including zoo animals, ornamental fish, parrots, ferrets, and guinea pigs. Some animals of agricultural importance, such as sheep, goats, catfish, and honeybees, are also classified as minor species.

The new law is expected to benefit people who own small or unusual pets, such as guinea pigs or ornamental fish, and to help zoo veterinarians treat their animals. Before this legislation, pharmaceutical companies could rarely afford to bring to market drugs for novel pets and zoo animals because the markets were too small to generate an adequate financial return. The new law modifies provisions of the Federal Food, Drug, and Cosmetic Act to provide some flexibility in getting limited-use drugs to market.

"This is an excellent law that will help veterinarians better serve zoo animals, endangered species, and many other minor species," says Linda Tollefson, D.V.M., deputy director of the FDA's Center for Veterinary Medicine.

The official name of the law is "The Minor Use and Minor Species Animal Health Act of 2004." Minor use drugs are drugs for use in major species that are needed for diseases that have a limited geographic range or affect a small number of animals.

Number of Americans With High Blood Pressure Rose in Last Decade

The number of adults in the United States with high blood pressure increased by 30 percent between 1988 and 2000, according to a study that analyzed government health statistics and other data gathered nationwide during the period.

The study found that at least 65 million Americans have hypertension, defined as blood pressure of 140/90 millimeters of mercury (mm Hg) or higher, using blood-pressure-lowering medications, or having been told at least twice by a physician or other health professional that they had high blood pressure. By that definition, almost a third of U.S. adults have hypertension.

"The bottom line is that the estimated number of adults with high blood pressure has increased," says Larry E. Fields, M.D., lead author of the study and senior executive advisor to the assistant secretary of the Department of Health and Human Services.

"High blood pressure is a major risk factor for coronary heart disease, kidney failure, heart failure, stroke, and other conditions. From a public and health professional perspective, it is important to be aware of high blood pressure, to have blood pressure checked regularly, and, if blood pressure is elevated, to initiate appropriate counseling and treatment," he says.

The findings came from an analysis of data from the U.S. Census Bureau and the 1999-2000 National Health and Nutrition Examination Survey (NHANES) IV, which included 4,531 people. The study was limited to people at least 18 years old. The new estimate is much higher than the previous NHANES report, based on data gathered between 1988 and 1994, which estimated that at least 50 million U.S. adults had high blood pressure.

Blood pressure values were based on three measurements that a physician took during a single visit to a mobile examination center.

Fields and his associates estimated that 59.2 million people had hypertension on the basis of blood pressure measurements or prescriptions for blood pressure medication. More than 6 million people had high blood pressure based on their medical history, resulting in an estimated total of 65.2 million hypertensive adults.

The 1999–2000 survey shows that 28.7 percent of women and 28.3 percent of men have high blood pressure. When prevalence was divided along racial and ethnic categories, non-Hispanic black Americans have the highest prevalence at 38.8 percent. High blood pressure is prevalent in 28.7 percent of the Mexican-American population, and in 27.2 percent of the non-Hispanic white population.

The study, published in the Aug. 24, 2004, issue of Hypertension, did not specifically examine potential reasons for the increased prevalence of high blood pressure. However, the investigators cited the aging of the U.S. population and the growing proportion of overweight and obese Americans as potential major contributors.

"It has been demonstrated that interventions that center on health behavior, such as getting regular physical activity, controlling weight, and eating a nutritious diet that includes lots of fruits and vegetables and moderate amounts of salt, can reduce a person's chances of developing high blood pressure," says Fields.
A new study of older women indicates that regular walking is not just good for the body; it's good for the brain.

Researchers at the Harvard School of Public Health and three other institutions tracked the exercise habits of more than 18,000 older women over a period of eight to 15 years. Then, when the women reached age 70 and older, the researchers tested the women's cognitive abilities—their memory, learning, and attention—over a two-year period. They found that women who performed a moderate amount of activity, walking two to three hours at an easy pace every week, performed significantly better on these tests of cognition than women who walked less than one hour per week.

Women who engaged in the most activity—for example, walking at least six hours per week—had a 20 percent decrease in risk of cognitive impairment compared to those who were inactive, and they also demonstrated the cognitive functioning of someone three years younger than their actual age.

"Walking is a popular, accessible, and inexpensive activity for older adults that appears to provide many health benefits," says lead author Jennifer Weuve, Sc.D., of the Harvard School of Public Health. "In addition to studies showing a reduced risk of heart disease, pulmonary disease, and diabetes, a moderate level of walking also appeared to reduce the rate of cognitive decline in our study. What is most striking is that for older women who are able to engage in several hours per week of physical activity, their cognitive function seemed to be comparable to that of a woman several years younger."

Weuve and colleagues at Brigham and Women's Hospital in Boston analyzed the data from 18,766 U.S. women, ages 70 to 81 years, from the Nurses' Health Study. Women were assessed twice, two years apart, on general cognition, verbal memory, category fluency, and attention. They found that women who were more active and participated in activities that ranged from walking at an easy pace to jogging experienced less cognitive decline than women who were not active.

Overall, the researchers found that the more active the individuals, the better their cognitive performance and the less decline they seemed to have. The findings are published in the Sept. 22, 2004, issue of the Journal of the American Medical Association.

"This is one of the first studies to explore the specific link between walking and cognitive function," Weuve says. "The health benefits of walking are becoming well-established and [this study] should provide older people with additional evidence to help encourage them to engage in walking or another form of physical activity."

Adults ages 65 years and older are the fastest-growing population in the United States and are at a high risk for dementia. Monitoring cognitive functioning and reducing risk factors associated with dementia are imperative to slowing its development.

The Nurses' Health Study was established in 1976 to study the relationship between the use of oral contraceptives and cigarette smoking and the risk of major illnesses. For a variety of reasons, including the dedication and commitment of the participants, the scope and range of the study has broadened over time to evaluate the implications of various lifestyle factors such as exercise and diet on women's health.
Avoid
DEEP VEIN THROMBOSIS

Keep the Blood Flowing

By Linda Bren

Holiday travelers will soon clog the nation's highways and inundate its airports in numbers not seen in recent years. The number of travelers over the four-day Thanksgiving holiday is expected to surpass the 31 million Americans who traveled more than 50 miles by car and the 5 million who went by plane in 2003, according to AAA spokesman Lon Anderson. "This is the first year we've seen travel returned to what it was pre-9/11," he says.

No matter what the mode of transportation, sitting motionless for long periods may put some travelers at an increased risk for deep vein thrombosis (DVT), a blood clot in a vein deep within the muscles, usually in the calf or thigh. But people can reduce their risk of getting DVT, says the American Heart Association (AHA), by taking some simple precautions on long trips.

The AHA estimates that 1 out of every 1,000 Americans develops DVT each year. "It oftentimes gives you a swollen, painful leg, usually in the calf," says Richard Stein, M.D., a cardiologist and associate chair of medicine at Beth Israel Medical Center in New York City and a spokesman for the AHA. "But it can be silent," producing no noticeable signs. "Tragic cases are when ... a piece of thrombus [blood clot] breaks off and goes into the lungs," says Stein. This complication of DVT, known as pulmonary embolism, was brought to public attention in 2003 when it caused the death of 39-year-old NBC reporter David Bloom. Bloom had spent long hours reporting the war in Iraq from the cramped quarters of a military vehicle.

Any long period of immobility—such as being bedridden from illness, recovering from surgery, or sitting for extended periods while traveling—is a risk factor for DVT and pulmonary embolism, says the National Heart, Lung, and Blood Institute (NHLBI). DVT can also develop in other instances when the blood flow in the legs is restricted and slows down.
Restricted flow may occur with certain types of cancer and cancer treatment, obesity, inherited clotting disorders, pregnancy, and damage to the veins following injury or orthopedic surgery.

Clotting the blood is "nature's way of trying to prevent bleeding," says Wolf Sapirstein, M.D., a cardiologist at the Food and Drug Administration. But when nature's protective mechanism overcompensates and precautions aren't taken, there is a danger of blood clots.

Reducing the Risk While Traveling
DVT has been dubbed "economy-class syndrome," reflecting the cramped legroom in economy class airline seating. But it can happen to passengers in any seating class of an aircraft, according to the Federal Aviation Administration. It can also happen to people on long rides in cars, trains, or buses.

"People should not be afraid to travel," says Stanley Mohler, M.D., professor emeritus of aerospace medicine at the Wright State University School of Medicine in Dayton, Ohio. "They should just anticipate that they may be inclined to be immobile," he says, and take precautions. A two-hour flight wouldn't be a problem, he says, but a 12-hour flight would be "a big problem" if a person sits inactive the entire time. Children who travel don't appear to be at risk for DVT, says Mohler, because they are generally more active in their seats than adults.

In adults, "hub-and-spoke flying is also a problem," he says, referring to a series of connecting flights interspersed with long hours of waiting between flights. "It's important for passengers to keep moving their legs to help the blood flow," even when waiting in the airport terminal, says Mohler, who advises walking when possible. "When you walk, the muscles of the legs squeeze the veins and move blood to the heart."

Another way to help move blood to the heart is to wear compression stockings, which put gentle pressure on the leg muscles. Studies in healthy people have shown that wearing compression stockings minimizes the risk of developing DVT after long flights, according to the AHA. These stockings are available at medical supply stores.

Stein advises avoiding regular socks with very tight elastic bands at the top and sitting with your legs crossed for long periods of time, which constricts the veins. He also urges travelers who can't walk around frequently to exercise their legs by curling or pressing the toes down, which causes the muscles to contract and squeeze on the leg veins, helping to pump the blood along.

Airlines, also, are encouraging passengers to periodically move and stretch their legs. The Australian carrier Qantas, for example, offers leaflets with leg exercises that passengers can do in their seats. Qantas began printing warnings for DVT on its tickets following the highly publicized death of a 28-year-old woman in October 2000. The woman died from a pulmonary embolism shortly after she stepped off a 20-hour Qantas flight from Australia to England after attending the Olympic Games in Sydney.

Stein also advises drinking plenty of fluids to prevent dehydration. Dehydration causes blood vessels to narrow and blood to thicken, increasing the risk for DVT. Reducing alcohol and coffee consumption, which both contribute to dehydration, is also recommended. These steps aren't scientifically proven to prevent DVT, but they're common sense, says the AHA. As for taking aspirin to prevent DVT, "there is no real evidence that an aspirin reduces the likelihood, but it very possibly could be of value," says Stein.

When traveling by car, "Don't take a 10-hour trip without stopping every couple of hours," says Stein. "Get out and walk a bit." Even if you're the driver, you still need to take walking breaks, he says. "Pushing on the gas pedal isn't enough activity even for the one leg."

"Deep vein thrombosis went unrecognized for decades because the clots that formed in the large veins in the legs often started coming off in little pieces after a person had been home for a day or two," says Mohler, "so they would go to the emergency room with a suspected possible heart attack."
Chest pain can be a symptom of both heart attack and pulmonary embolism. Other common symptoms of pulmonary embolism are unexplained shortness of breath and coughing up blood. It’s important to tell your doctor if you have any symptoms of pulmonary embolism, sit down and tell someone you have an emergency and need immediate help, says Stein. At that point, “there is no value in putting your feet up or drinking gallons of water. Getting to an emergency room quickly is your best shot.”

Another potential complication of DVT is post-phlebitic syndrome, a permanent condition caused by valves in the leg veins that don’t work properly. “The body has mechanisms within itself to dissolve clots, but it’s a very slow process,” says George Shashaty, M.D., an FDA hematologist. “In the interim, an inflammatory reaction occurs that can scar the veins, especially the valves.” The valves then fail to prevent blood from flowing backwards, allowing the blood to pool in the leg veins and cause pain, swelling, and sometimes varicose veins and skin ulceration.

Diagnosis and Treatment

A commonly used FDA-approved medical test to diagnose DVT is the duplex ultrasound, says Sapirstein. A handheld device is passed back and forth on the surface of the affected area, sending sound waves from the body to a machine that generates and displays a picture of the blood flow on a video screen for a doctor to evaluate.

Another less commonly used test, venography, may be done to diagnose DVT if ultrasound does not give a clear diagnosis, says Sapirstein. A dye is injected into a vein, which makes the blood flow visible when an X-ray is taken.

Duplex ultrasound, chest X-rays, and other tests may be used to diagnose a pulmonary embolism.

“The primary treatment for deep vein thrombosis and pulmonary embolism is blood thinners,” says Sapirstein. Blood thinners, or anticoagulants, such as heparin, will not dissolve clots already formed, but will keep them from growing and prevent new ones from forming. Heparin may be given as an injection below the skin surface or into a vein (intravenously).

People at risk for DVT may be prescribed the blood thinner Coumadin (warfarin) to keep clots from growing. Warfarin is currently the only FDA-approved blood thinner taken orally. “Other agents are being developed as oral anticoagulants but aren’t on the market yet,” says Kathy Robie-Suh, M.D., Ph.D., an FDA internist. Warfarin interacts with many other medications. “If you are on warfarin, the doctor needs to know all the other medications you are on, including over-the-counter,” says Robie-Suh, and patients should make sure they take their warfarin before going on a trip. People who have had one deep vein clot are prone to getting more.

“When a patient cannot tolerate blood thinners or continues to develop clots, then you have to go to an alternative, such as a filter,” says Sapirstein. The FDA has cleared medical filters, such as “umbrella filters,” that a surgeon can insert into the vena cava, a large vein in the abdomen that returns oxygen-depleted blood to the heart. The filter is inserted in a folded position and then springs open against the vein walls to keep the vein open for blood flow. The filter does not keep blood clots from forming, but it prevents their passage from the veins in the lower extremities to the heart and lungs. These filters may either remain in place permanently or be removed later.

Another treatment alternative for pulmonary embolisms is administering one of the FDA-approved thrombolytics. These potent drugs, known as “clot-busters,” are given intravenously to quickly dissolve large clots that are unlikely to break up on their own. They are used only in life-threatening situations because they may cause sudden and severe bleeding.

What Makes Deep Vein Thrombosis More Likely?

- an inherited condition that causes increased risk for clotting
- low blood flow in a deep vein due to injury, surgery, or being immobile
- cancer and its treatment
- other medical conditions, such as varicose veins
- sitting for a long period of time, as on long trips
- pregnancy and the first six weeks after giving birth
- being older than age 60
- being overweight
- taking birth control pills or hormone therapy
- having a medical condition that requires a tube placed in a vein to allow easy access to the bloodstream for medical treatment (central venous catheter).

Source: National Heart, Lung, and Blood Institute

Facts About Deep Vein Thrombosis and Pulmonary Embolism

- Nine out of 10 cases of pulmonary embolism are caused by blood clots that form in the legs and then travel to the lungs.
- More than 600,000 people in the United States have a pulmonary embolism each year, and more than 10 percent of them die from it.
- Most who die do so within 30 to 60 minutes after symptoms start.
- Pulmonary embolism occurs equally in men and women.
- The risk of having a pulmonary embolism doubles for each 10 years after age 60.

Source: National Heart, Lung, and Blood Institute
Merck Withdraws Vioxx; FDA Issues Public Health Advisory

The Food and Drug Administration has issued a public health advisory to inform people of the voluntary withdrawal from the market of Vioxx (rofecoxib) by its maker, Merck & Co. Inc., on Sept. 30, 2004.

The agency advisory says people who used the nonsteroidal anti-inflammatory drug (NSAID) should consult with a physician about alternative medications. Merck withdrew Vioxx from the market after the data safety monitoring board overseeing a long-term study of the drug recommended that the study be halted. The board found an increased risk of serious cardiovascular events, including heart attacks and strokes, among study patients taking Vioxx compared with those receiving an inactive pill (placebo). The study was being done in patients at risk of developing recurrent colon polyps.

"Merck did the right thing by promptly reporting these findings to FDA and voluntarily withdrawing the product from the market." Acting FDA Commissioner Dr. Lester M. Crawford said. "Although the risk that an individual patient would have a heart attack or stroke related to Vioxx is very small, the study that was halted suggests that, overall, patients taking the drug chronically face twice the risk of a heart attack compared to patients receiving a placebo."

Crawford added that the FDA will closely monitor other drugs in this class for similar side effects. "All of the NSAID drugs have risks when taken chronically, especially of gastrointestinal bleeding, but also liver and kidney toxicity. They should only be used continuously under the supervision of a physician."

The FDA approved Vioxx in 1999 for the reduction of pain and inflammation caused by osteoarthritis, as well as for acute pain in adults and for the treatment of menstrual pain. It was the second of a new kind of NSAID (COX-2-selective) approved by the FDA. Subsequently, the FDA approved Vioxx to treat the signs and symptoms of rheumatoid arthritis in adults and children.

At the time that Vioxx and other COX-2-selective NSAIDs were approved, it was hoped that they would have a lower risk of gastrointestinal ulcers and bleeding than other NSAIDs, such as ibuprofen and naproxen. Vioxx is the only NSAID demonstrated to have a lower rate of these side effects.

In June 2000, Merck submitted to the FDA a safety study called VIGOR (Vioxx Gastrointestinal Outcomes Research) that found an increased risk of serious cardiovascular events, including heart attacks and strokes, in patients taking Vioxx compared with patients taking naproxen. After reviewing the results of the VIGOR study and other available data from controlled clinical trials, the FDA consulted with its Arthritis Advisory Committee in February 2001 regarding the clinical interpretation of this new safety information.

In April 2002, the FDA implemented labeling changes to reflect the findings from the VIGOR study. The labeling changes included information about the increase in risk of cardiovascular events, including heart attack and stroke.

Recently other studies in patients taking Vioxx have also suggested an increased risk of cardiovascular events. The FDA was in the process of carefully reviewing these results to determine whether further labeling changes were warranted when Merck informed the agency of the results of the new trial and its decision to withdraw Vioxx from the market.

For More Information
FDA information page on Vioxx
www.fda.gov/cder/drug/infopage/vioxx/

Merck news release on Vioxx
www.vioxx.com/rofecoxib/vioxx/consumer/
In October 2004, Chiron Corp. notified U.S. public health officials that none of its influenza vaccine, Fluvirin, would be available for distribution in the United States for the 2004–2005 influenza season. This reduces the expected supply of inactivated vaccine used in flu shots, since Chiron would have provided between 46 million and 48 million doses. The company's action came after the Medicines and Healthcare products Regulatory Agency in the United Kingdom had suspended Chiron's license to manufacture Fluvirin in its Liverpool, England, facility for three months.

The remaining influenza vaccine expected to be available in the United States this season is about 54 million doses of Fluzone, manufactured by Aventis Pasteur. In addition, approximately 1.1 million doses of FluMist (influenza virus vaccine live, intranasal), manufactured by MedImmune, will be available.

Because of this urgent situation, the CDC, in coordination with its Advisory Committee on Immunization Practices, has issued interim recommendations about who should be vaccinated with the flu shot this flu season. People who are not included in one of the priority groups should forgo or defer vaccination so that the most vulnerable populations can be vaccinated.

**Priority groups who should be vaccinated with the flu shot this season:**
- all children ages 6 months to 23 months
- adults ages 65 years and up
- people ages 2 to 64 with underlying chronic medical conditions
- all women who will be pregnant during the flu season
- residents of nursing homes and long-term care facilities
- children ages 6 months to 18 years who are on chronic aspirin therapy
- health care workers with direct patient care
- out-of-home caregivers and household contacts of children younger than 6 months.

**Other vaccine recommendations:**
- Healthy people who are ages 5 to 49 and not pregnant, including health care workers (except those who care for severely immunocompromised patients in special care units) and persons caring for children under 6 months should be encouraged to be vaccinated with FluMist.
- People in the priority groups identified above should be encouraged to search locally for vaccine if their usual health care provider doesn't have vaccine available.
- Many children under age 9 require two doses of vaccine if they have not been previously vaccinated. All children at high risk of complications from influenza, including those ages...
Vaccination is the primary way to prevent the flu, and it lowers rates of illness, hospitalization, and deaths. The flu season in the United States typically runs from November to April.

The flu, a contagious respiratory illness caused by the influenza virus, is spread mainly from person to person through coughing, sneezing, and touching contaminated surfaces, such as doorknobs. The main symptoms are fever, headache, fatigue, body aches, cough, sore throat, and congestion.

Most people get over the flu in about a week, but it can lead to ear infections, bronchitis, pneumonia, and other complications. Each year, the illness causes an average of 36,000 deaths and more than 200,000 hospitalizations. Most deaths occur in people with heart or lung diseases. Several studies have shown that children younger than 2, even if they are healthy, are more likely to be hospitalized when they have the flu than older children.

Last season, the CDC received reports of 152 flu-related deaths in children under 18. Most were younger than 5. Almost half had an underlying medical condition, but 40 percent were apparently healthy. Of the 135 children who died who could have been vaccinated, only five were adequately vaccinated against the flu.

Children ages 6 months and older can get the injectable flu shot, which contains dead influenza virus. It is not approved for use in children younger than 6 months. Two doses of inactivated flu vaccine given 30 days apart are recommended for previously unvaccinated children younger than 9.

Flumist (influenza virus vaccine live, intranasal), which is sprayed into both nostrils and contains weakened live virus, is not approved for use in children younger than 5. Two doses of live flu virus vaccine given 60 days apart are recommended for previously unvaccinated children younger than 9. Flumist is approved for use in healthy people ages 5 to 49 who are not pregnant.

Along with warding off flu through vaccination, people can lower the risk of infection by washing their hands frequently, covering their mouths and noses when sneezing or coughing, and avoiding close contact with people who are sick with the flu.

6 months to 23 months, should be vaccinated with a first or second dose, depending on vaccination status. However, doses should not be held in reserve to ensure that two doses will be available. Rather, available vaccine should be used to vaccinate people in priority groups on a first-come, first-served basis.

Who should not get flu vaccine:
- People who have a severe allergy to chicken eggs should not get a flu vaccination.
- It is prudent for people who previously developed Guillain-Barré syndrome in the six weeks after getting a flu shot to avoid vaccination.

For More Information
CDC Web site
www.cdc.gov/flu/

FDA Web site
www.fda.gov/oc/opacom/hottopics/flu.html

CDC hotline
(888) 246-2675 (English)
(888) 246-2857 (Spanish)

Jesse Goodman, M.D., M.P.H., of the FDA answers a question during a news conference on the unavailability of flu vaccine manufactured by Chiron Corp., as HHS Secretary Tommy G. Thompson (center) and other public health officials look on.
Due Tuesday:
- Read *The Little Monster: Growing Up With ADHD*

Whiteboard:
- 1980s
- AD
- ADHD
- ADHD-C
- ADHD-Res

Other:
- ADHD-Res (not otherwise specified)
ADHD: Not Just for Kids Anymore

By Linda Bren

It seemed that the harder he tried, the worse things got for Robert Jergen. As a child, he was always being scolded by his parents and teachers. As an adult, his bosses reprimanded him for missed deadlines and his attitude problem. He got fired from jobs, drank heavily, and lost his fiancé.

But Jergen wasn't a slouch, a drunk, or intentionally obnoxious. He had a condition called attention-deficit hyperactivity disorder (ADHD).

"I wanted to be a good kid, but I frequently did things without thinking or without even realizing that I did them," says Jergen. Problems with concentration continued to plague him as an adult. In college, Jergen would stay up all night trying to finish his schoolwork. "I could not focus my attention on the page long enough to read a paragraph. My thoughts raced round and round in my head. It's like my mind was a pinball machine with five or six balls smashing into each other."

Robert Jergen, who has ADHD, has developed strategies to help him concentrate on his work as a college professor, lecturer, and author.
ADHD is the most commonly diagnosed mental health disorder in children, according to the American Psychiatric Association. It's often diagnosed once a child hits preschool and is disruptive in class—unable to sit still, talking incessantly, and having emotional outbursts. While some children see their symptoms fade as they get older, others carry them into adolescence and adulthood.

Although there is no cure for ADHD, medications and behavioral therapy can help treat the symptoms. The Food and Drug Administration has approved two drugs for adults with ADHD, and more have been approved for use in children. But the decision to take medication should be considered carefully and discussed with a health professional, says Paul Andreason, M.D., a drug reviewer in the FDA's Division of Neuropharmacological Drug Products. Some drugs used to treat ADHD can be dangerous for adults with certain medical conditions. They also have the potential for addiction and abuse. Adults taking medications should be closely monitored by a physician. Children, too, who take drugs for ADHD need regular medical checkups.

**Three Types of ADHD**

Everyone has trouble sitting still sometimes, or managing time, or completing a task. But the behavior of people with ADHD goes beyond occasional fidgeting, disorganization, and procrastination. For them, performing tasks can be so hard that it interferes with their ability to function at work, at home, at school, and socially.

A diagnostic manual compiled by the American Psychiatric Association identifies three types of ADHD: inattentive, hyperactive-impulsive, and combined.

A person with inattentive ADHD, previously known as attention-deficit disorder (ADD), has trouble focusing on activities, organizing and finishing tasks, and following instructions.

Children with hyperactive-impulsive ADHD are in constant motion, dashing around touching everything in sight, and jumping on and off furniture. They often blurt out inappropriate comments, don’t wait their turn, show excessively intense emotions, or hit others when upset. Hyperactive and impulsive adults feel restless, are constantly “on the go,” and try to do multiple tasks at once. They are often perceived as not thinking before they act or speak.

Individuals with the combined form of ADHD show symptoms of both inattention and hyperactivity-impulsivity.

**Who Has It?**

The National Institute of Mental Health (NIMH) estimates that between 3 percent and 5 percent of children in the United States have ADHD. This means that in a classroom of 25 to 30 children, it is likely that at least one will have ADHD. Three times as many boys are diagnosed with ADHD, but “girls are getting diagnosed more and more,” says Nora Galil, M.D., a psychiatrist in private practice in Washington, D.C. The symptoms may be easier to spot in boys, she says, who may be seen slipping from their chairs and tossing things across the room. “You can often identify it in a short period of time because they are so disruptive. Girls may be the ones who daydream and are not disruptive, so it’s not picked up nearly as much.”

The number of adults with ADHD is unknown, and medical experts continue to debate whether children can expect to outgrow the symptoms of ADHD by the time they reach adulthood.

Some studies have shown a significant decline in ADHD symptoms as a person ages. Others estimate that between 30 percent and 70 percent of children with ADHD will continue to have symptoms into adulthood.

“In adults, it’s a much more elaborate disorder than in children,” says Russell Barkley, Ph.D., a psychiatry professor at...
the Medical University of South Carolina. “It’s more than paying attention and controlling impulses. The problem is developing self-regulation.” This self-control affects an adult’s ability not just to do tasks, but to determine when they need to be done, says Barkley. “You don’t expect 4- or 5-year-olds to have a sense of time and organization, but adults need goal-directed behavior—they need help in planning for the future and remembering things that have to get done.”

The Consequences of ADHD

Whether in a child or an adult, ADHD can have serious consequences. Some studies show that children with ADHD have more emergency room visits than their non-ADHD peers. Adolescents with ADHD are more likely to engage in risky behavior, leading to substance abuse, sexually transmitted diseases, and teen pregnancy. Adolescents and young adults are more likely to drop out of school and less likely to enter and graduate from college, according to some studies. And adults with ADHD are more likely to suffer from depression and anxiety, be fired from jobs, and get divorced than non-ADHD adults.

Teens and adults with ADHD have 2 to 3 times more auto accidents and twice the number of severe accidents resulting in vehicle damage and bodily injury as those without ADHD, according to studies done by Barkley and others. “They have coordination deficits, less skill in maneuvering vehicles in traffic, slower reaction time, and inattention,” says Barkley.

People with ADHD often have “a huge issue of self-esteem,” says Galil. “They may have been underachievers and told ‘you’re so smart, why can’t you do this? You’re not trying hard enough.’”

Jergen says he always tried very hard, but he couldn’t focus his mind on the task at hand. He likens it to having a song or jingle in your head for days at a time, but “add three or four or five more thoughts to the mix and amplify them. Spin them round and round and round in your head and make them go faster and faster and faster until they become like an all-consuming obsession. Everything centers on those thoughts. You can’t focus on anything else. You can’t escape them.”

Not a Discipline Problem

ADHD was once looked upon as a discipline and behavioral problem resulting from bad parenting. Some suggested it was caused by high sugar intake, food additives, excessive TV viewing, and family problems. But none of these explanations is supported by scientific evidence.

Most scientists agree that it’s a biologically based disorder of the nervous system. Brain imaging research using a technique called magnetic resonance imaging (MRI) has shown that differences exist between the brains of children with and without ADHD, but the exact mechanism of brain function causing the symptoms of ADHD is unknown. Scientists caution that MRIs used in studies are research tools and cannot be used to diagnose ADHD in a specific person.

Recently published research suggests that ADHD tends to run in families. In these studies, children with ADHD have, on average, at least one close relative with ADHD. Over the years, other theories have suggested that exposure

How is ADHD Diagnosed?

According to the American Psychiatric Association, a person is diagnosed with ADHD if

- they often have either six inattention symptoms or six hyperactivity and impulsiveness symptoms
- symptoms continue for at least six months and are more frequent and severe than normal
- symptoms cause significant damage to social, academic, or work functioning
- some damage to functioning occurs in at least two settings, such as home, work, or school
- some damaging symptoms occurred before age 7
- the symptoms are not due to another disorder.

Inattention Symptoms

- does not pay close attention to details or makes careless mistakes
- has trouble keeping attention on activities
- does not seem to listen when spoken to directly
- does not follow through on instructions and fails to finish tasks
- has difficulty organizing tasks and activities
- avoids, dislikes, or is reluctant to do tasks requiring sustained mental effort
- loses things necessary to do tasks or activities
- is easily distracted
- is forgetful in daily activities.

Hyperactivity or impulsiveness symptoms

- fidgets with hands or feet or squirms in seat
- leaves seat at times when remaining seated is expected
- feels restless, or, in a child, inappropriately runs about or climbs excessively
- has difficulty taking part in leisure activities or playing quietly
- is “on the go” or acts as if “driven by a motor”
- talks excessively
- blurts out answers before questions have been completed
- has difficulty awaiting turn
- interrupts conversations or intrudes on others’ activities.

Source: APA
to lead in the environment, premature birth, birth trauma, and brain injury may lead to the development of ADHD. Some studies have shown a possible correlation between the use of cigarettes and alcohol during pregnancy and the risk for giving birth to a child with ADHD. For this and many other health reasons, the NIMH recommends that women who are pregnant refrain from both cigarette and alcohol use.

**Diagnosing ADHD**

There is no single test to determine if a person has ADHD. A specialist makes the diagnosis by comparing a person’s pattern of behavior against a set of criteria established by the American Psychiatric Association.

“Sometimes teachers may identify a child as potentially having ADHD,” says Galil. “Parents will not always know because they organize and structure and manage so much of the child’s life, it masks what’s going on.”

Although teachers and parents may recognize some symptoms, it’s important to get a diagnosis from a health professional, ideally one with training in ADHD and mental disorders, says the NIMH. This may be a psychiatrist, psychologist, behavioral neurologist, or a developmental or behavioral pediatritian. More than one health professional may be consulted to diagnose and treat ADHD, since medical and psychological tests, medication, and counseling may be involved.

“Many health professionals believe that ADHD is over-diagnosed,” says Andreason, and doctors need to consider the complete history of patients before diagnosing them.

“It’s a hard diagnosis to tease out, and we need to spend some time asking questions about all areas of their life,” adds Edmund Higgins, M.D., clinical assistant professor of family medicine and psychiatry at the Medical University of South Carolina and a psychiatrist in private practice.

Some adults may discover they have ADHD only after their children are diagnosed with the disorder. That’s how Toni Wood found out she had it.

Wood, of Chesapeake, Va., was a hyperactive child, always getting into trouble at school and always in the principal’s office, she says. “If I was quiet, I was sick.” Throughout her school years, she had a hard time processing information and asked a lot of questions in class. “I really frustrated me, and everybody was looking at me and rolling their eyes. I knew I wasn’t stupid, but I was always behind.”

Wood persevered, graduating from high school, serving in the U.S. Coast Guard, and going to college. Civilian life was daunting for her after the structured military environment where “they told you what to wear and what to do,” says Wood. She graduated from college, but continued to have difficulty with daily activities—paying bills and completing tasks, especially in the evening when she was most fidgety and inattentive. “I thought I was going crazy,” she says.

At age 38, Wood found out that she wasn’t crazy. After both her sons were diagnosed with ADHD, Wood’s doctor diagnosed her with the condition, too. She felt a weight being lifted off her shoulders, she says. “I’m not using ADHD as an excuse; it’s an explanation. Now I understand why.”

**What’s It Like Having ADHD?**

“... It’s like being super-charged all the time. You get one idea and you have to act on it, and then, what do you know, but you’ve got another idea before you’ve finished up with the first one, and so you go for that one, but of course a third idea intercepts the second, and you just have to follow that one, and pretty soon people are calling you disorganized and impulsive and all sorts of impolite words that miss the point completely. Because you’re trying really hard. It’s just that you have all these invisible vectors pulling you this way and that, which makes it really hard to stay on task.”

Edward M. Hallowell, M.D., © 1992, used by permission. Hallowell is a psychiatrist in Sudbury, Mass., who has ADHD.

**Treatments for ADHD**

A number of FDA-approved medications are available to help treat the symptoms of ADHD. Some people have better results from one drug, some from another. “But treatments need to involve a behavior modification program,” says Andreason. “Medicine is only an adjunct to behavior modification.”

Children with ADHD may require emotional counseling and behavioral management involving parents, teachers, and health professionals. Adults with ADHD may benefit from counseling, vocational guidance, and professional coaching done by specialists who help individuals develop coping skills and methods for organization and time management.

Jergen has developed his own coping strategies, and daily exercise is an important one. “When my mind is in a fog, I get on the treadmill and break a sweat, the fog parts, and I can concentrate,” he says. He’s also set up his office environment with special lighting and soft music to help him relax and concentrate.

People with ADHD may be hyperactive, but, surprisingly, they are often prescribed a stimulant to help treat the symptoms. Stimulants can improve alertness and attention without making the hyperactivity worse.

FDA-approved stimulants for children ages 6 and older include products containing various forms of methylphenidate, amphetamine, and methamphetamine.

In August 2004, the extended-release form of the stimulant Adderall (Adderall XR), previously approved to treat children with ADHD, was also approved to treat adults with ADHD. An extended-release form of a drug works in the body over a longer time than an immediate-release form, allowing the medication to be taken less frequently.

Adderall or other stimulants should not be taken by people with certain conditions, including hyperthyroidism, glaucoma, moderate-to-severe hypertension, other heart-related conditions, or a history of drug abuse.
Some common side effects of stimulants are insomnia, decreased appetite, and increased anxiety or irritability. Children who take stimulants may grow and gain weight more slowly, and growth should be monitored by their pediatricians.

Because stimulant medicines have a high potential for abuse, the U.S. Drug Enforcement Administration has placed stringent controls on them. For example, the DEA requires special licenses to manufacture, distribute, and prescribe these controlled substances, and prescription refills aren’t allowed.

One other drug, Strattera (atomoxetine), is FDA-approved for use in adults with ADHD as well as in adolescents and children ages 6 and older. Strattera is not classified as a stimulant and does not seem to have a potential for abuse. It is not classified as a controlled substance, so it can be prescribed with refills. Strattera causes the increase in heart rate and blood pressure and should be used with caution in people with hypertension or heart-related conditions. In clinical studies, the most common side effects of Strattera in adults were dry mouth, headache, insomnia, nausea, decreased appetite, and constipation. In children and adolescents, common side effects were stomachache, headache, and decreased appetite. Like stimulants, Strattera may slow weight gain and growth in children, and these measures should be monitored by a pediatrician.

**Treatment Decisions**

Galil, who treats both children and adults with ADHD, says she doesn’t use medications as frequently in adults. Parents bring children to her because they’re not doing well at school or their behavior is disruptive, she says, but adults who haven’t been diagnosed as children often “have found ways to cope without medication for years.” Sometimes, she’ll prescribe a stimulant as needed for specific tasks, such as for an events planner who was “marvelous at events with a headset on and 4,000 people around her, putting out a fire a minute,” but didn’t do well sitting back at the home office doing paperwork. So she’d take medication on a day that she needed to spend time on paperwork.

“With children, it’s different,” says Galil. “They often benefit from medication seven days a week. Adults, by and large, don’t want to be on medication all the time.” But with diagnosis and treatment, “some who never finished college or graduate school now have the tools to go back and finish.”

Wood is one of these. Since she’s been on medication, she went back to college and earned a second degree. “I saw such a difference,” she says. “College was so much easier” and so were routine household tasks, like paying bills. Wood is now an ADHD coach, helping other people cope with the disorder.

Once he was diagnosed with ADHD at age 24, Jergen said it took about two years of trying different medications and dosages to find out what worked best for him. Like Wood, he found that tasks became easier for him. He got his doctorate in special education,
ADHD. Jergen urges parents of children with ADHD to help them use the energy to be productive instead of making them slow down.

After 10 years of taking various stimulants, antidepressants, and mood stabilizers, Jergen went off medications in 2002 because of their sexual side effects and the development of a vocal tic that caused him to make involuntary noises. He continues teaching and writing, recently got married, and says, “My life is just fantastic.”

“I’m still hyperactive, impulsive, and inattentive,” adds Jergen. “If I were an air traffic controller, planes would be crashing.” But Jergen, known as a dynamic speaker, says he’s in his element in front of a class.

Drug Risks and Precautions

Public health officials are concerned that stimulants may be inappropriately prescribed for some adults with ADHD. "Stimulants do work, but we know that they increase blood pressure and pulse rate," says Andreason, which could lead to strokes and heart attacks. “These drugs are very strongly labeled for their risk to the cardiovascular system,” he adds.

"Patients with hypertension shouldn’t be getting stimulants," says Kate Gelperin, M.D., a medical officer in the FDA’s Office of Drug Safety. "If your blood pressure is on the high side, these drugs are not for you.” About one-third of U.S. adults have high blood pressure, according to a study published in the October 2004 issue of Hypertension, a journal of the American Heart Association.

Raymond Woosley, M.D., Ph.D., a clinical pharmacologist and vice president for health sciences at the University of Arizona, says, “There are a lot of people who don’t know they have hypertension or heart disease. In many people, the first symptom of heart disease is sudden death.” Woosley advises adults with ADHD who are prescribed stimulants to “make sure their doctor is fully informed of their total medical condition and get a complete medical workup to make sure they’re not at risk.”

Even those without hypertension who take stimulants may be at risk, says Gelperin. “It’s not known whether adults who take stimulants over long periods of time may have an increased risk of sudden death, stroke, or heart attacks,” she says, “although we do know that people who take an overdose of stimulants experience these adverse effects.”

Woosley also recommends that parents get their children checked by a qualified pediatrician before giving them stimulants for ADHD. Parents should not insist on a stimulant for their child based on the positive experience of a friend’s child who is taking the stimulant or because a teacher suggests it, he says. A child should be examined by a doctor and diagnosed with ADHD before being placed on a stimulant. "A stimulant given to a child with ADHD can help to normalize them,” he says, “but if given to someone who doesn’t have the right diagnosis, it can make them worse.” Once prescribed a stimulant, a child’s blood pressure and heart rate should be monitored closely until the dosage is stabilized, and then yearly, says Woosley, since the way the body responds to medication is highly variable and may change over time.

Research has shown that people with ADHD who take stimulants in the form and dosage prescribed do not appear to be at as great a risk for addiction as previously feared. However, when stimulants are abused, the consequences can be extremely dangerous—even deadly. According to the National Institute on Drug Abuse, taking high doses of a stimulant can cause an irregular heartbeat, dangerously high body temperatures, and heart failure or lethal seizures.

“The FDA has received many reports over the years describing serious adverse effects, including death, associated with stimulant abuse or overdose,” says Gelperin.

“Some people will like the effects of the stimulants—either performance enhancement or the euphoria—and will want to be diagnosed as having ADHD,” says Higgins. “Where I get concerned is when college students or even professionals come to me and say, ‘I have trouble with attention.’ Everyone has trouble with attention at some point—particularly with boring tasks.’ We need to separate patients with some symptoms of ADHD from those who have a genuine disorder, he says. Higgins is also troubled by parents who take their child’s stimulant or someone else’s and claim they feel better. “Stimulants are basically ‘speed,’” he says, “and most people will be more productive with them. That doesn’t mean they have a disorder.”

Higgins says that, in his practice, he reserves stimulants for people who have severe impairment, for whom Strattera doesn’t work, and who are not at risk for substance abuse.

For More Information

National Institute of Mental Health
(800) 615-6464
TTY: (301) 443-8431
www.nimh.nih.gov

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)
(800) 233-4050
www.chadd.org
The Importance of Public Comment to the FDA

By Carol Rados

Anyone can submit comments concerning new rules and regulations being considered by the U.S. Food and Drug Administration. And, these suggestions can and do influence the agency’s actions.

The FDA regulates the way that foods, drugs, medical devices, and other health products are produced and sold. FDA regulations have considerable impact on the nation’s health, industries, and economy. Violators can be fined, jailed, or forced to close their businesses.

FDA regulations are issued consistent with the Administrative Procedures Act, which governs the rulemaking process for federal agencies. The FDA encourages public comment on the agency’s proposed rules because the public has a vested interest in the products it regulates, and because the input provides critical insight into the effects of the regulation on the public. The comments often present the “real world” concerns of those who use the products.

For example, several years ago nutritionists, bread manufacturers, and consumer groups provided comments on which ingredients Americans wanted—or didn’t want—in white bread. The FDA adopted the standards only after taking into account the public’s comments and recommendations.

The FDA allows ample time for public input and carefully considers these comments when it draws up a final rule. "People don’t always understand that FDA’s decisions in response to comments aren’t just based on the number of comments, or ‘majority rules,’” says Edwin V. Dutra Jr., director of the FDA’s Regulations Policy and Management Staff. “When a consumer sends in a comment based on sound grounds, that comment can definitely make a difference in the agency’s decision-making.”

How to Comment

When the FDA plans to issue a new regulation or revise an existing one, it places an announcement in the Federal Register—one of the most important sources for information on what the agency is doing—on the day the public comment period begins. The agency also posts the proposal on its Web site at www.fda.gov/ohrms/dockets/. The “notice of proposed rulemaking” describes the planned regulation and provides background on the issue. It also gives the addresses for submitting written and electronic comments and the name of a person to contact for more information.

Also noted is the “comment period,” which specifies how long the agency will accept comments from the public. Usually, the file—a docket—stays open for comments for at least 60 days, though some comment periods are as short as 10 days or as long as nine months.

Anyone can ask agency officials to extend a comment period by submitting a written request if they do not think there is sufficient time to study the proposal and comment on it. But there must be good reason to support the request. If the agency grants the extension and allows more time for the public to comment, a notice is published in the Federal Register.

There is no special form to fill out for comments, nor do submitters have to
follow a certain style. But the FDA can process comments most effectively if they are presented—either handwritten or typed—on 8 1/2 by 11-inch paper. Comments can be mailed to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852, or submitted through an e-mail to fdadockets@oc.fda.gov. Comments also can be submitted online at www.fda.gov/dockets/ecomments.

Submissions should include the commenter’s name and address. Anonymous submissions will not be accepted. The following information is also recommended for making effective comments:

- Clearly indicate if you are for or against the proposed rule or some part of it, and why. Agency reviewers look for good science and good reasoning in the comments they evaluate.
- Refer to the docket number listed in the Federal Register notice.
- Include a copy of articles or other references that support the comments. Only relevant material should be submitted.
- If an article or reference is in a language other than English, it must be accompanied by an English translation, verified to be accurate. This would include providing the name and address of the translator and a brief statement of his or her qualifications. Translations should be accompanied by a copy of the original publication.
- To protect privacy when submitting medical information, delete names or other information that would identify patients.
- Comments that are mailed must be postmarked, or e-mails dated, by the last day of the comment period. Comments that are delivered in person must be received by the FDA by the last day of the comment period.

The number of comments received for proposed rules varies. For example, a rule that established reporting procedures for problems with medical devices attracted 300 comments, while a proposal to regulate tobacco generated more than 500,000 comments. Other proposals generate fewer comments, such as the 35 received on a proposal to change generic drug approvals.

However, this smaller number of comments still represented a wide range of companies, trade and consumer groups, and others.

What Happens Next

When the FDA receives a comment, it is logged, numbered, and placed in a file for that docket. But it also becomes public information, says Jennie C. Butler, director of the Division of Dockets Management. “All information provided is public and may be posted to the Internet,” she adds.

Under the Freedom of Information Act (FOIA), visitors to the FDA’s reading room, Room 1061, 5630 Fishers Lane, Rockville, Md., can receive free copies of up to 50 pages of comments if their request is for noncommercial use. After that, each page costs 10 cents. People also can send the FDA a FOIA request and have copies of comments mailed to them. For many significant proposals, the comments are available electronically over the Internet or may be available on a computer disk through a FOIA request.

After careful consideration of the comments and concerns on a proposed rule, the FDA usually will publish a final rule, unless a decision is made that the proposal should not be finalized. All proposed and final rules issued by the FDA are published in the Federal Register, issued Monday through Friday. Pending matters open to public comment often are reported by the news media and also can be found

### Submitting Comments to the FDA

**E-Comments**

View proposed FDA regulations: [www.fda.gov/ohrms/dockets/](http://www.fda.gov/ohrms/dockets/)

Online access to the Federal Register: "Reference Room" link at [www.fda.gov](http://www.fda.gov)

Submit comments online to: [www.fda.gov/dockets/ecomments](http://www.fda.gov/dockets/ecomments)

E-mail comments to: [fdadockets@oc.fda.gov](mailto:fdadockets@oc.fda.gov)

View pending federal government matters open to public comment at the federal e-rulemaking portal: [www.regulations.gov](http://www.regulations.gov)

**Comments by Mail**

Print or type on 8 1/2 by 11-inch paper and mail to:
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Questions?**

Call the Division of Dockets Management:
(301) 827-6860
Hours: Monday through Friday, 9 a.m. to 4 p.m.
Eastern time
on the FDA's Web site and the federal
gov.

**Other Opportunities to Comment**
Occasionally, says Butler, "There are
notices just calling for comments on a
particular subject, such as the docket
on obesity." Typically, this is known as
an "advance notice of proposed rule-
making," and these also appear in the
Federal Register. The advance notice is
often used when the agency has less
information about an issue, or if it
wants help in deciding what approach
to take about an issue. Generally, the
agency asks some questions, which
helps clarify what information it would
most like to obtain.

Questions about the comment pro-
cess should be directed to the FDA
Division of Dockets Management,
(301) 827-6860. Hours are 9 a.m. to
4 p.m. Eastern time, Monday through
Friday.

The Federal Register is available at
many public libraries and colleges,
and on the FDA Web site at www.fda.
gov. Under "Reference Room," click on
"Federal Register." ■

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**Statement of Ownership, Management, and Circulation**

(Required by 39 U.S.C. 3685)

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Raymond Formanek Jr., Editor
Facing Infertility

After trying unsuccessfully to conceive, Heather and Anthony Pansera turned to intrauterine insemination.
Heather Pansera and her husband, Anthony, started trying to have a baby as soon as they got married in 2000. In 2001, they settled into a new house in Canton, Ohio, with plenty of room to raise a family. One year passed, and Heather, 32, didn’t think much about it. Another year passed and she panicked.

“We were a couple for five years by the time we got married, so we decided to let nature take its course,” she says. “It never crossed our minds that getting pregnant would be so difficult.”

It seemed like everyone else was having babies, says Anthony, 39. “I have three brothers and three sisters, and they all had kids. You’re happy for other people, but you want to experience it too.”

An evaluation by a fertility specialist revealed no clear-cut reason for their inability to conceive naturally. What ultimately worked was a combination of a drug to induce ovulation and intrauterine insemination, a procedure in which a catheter was used to deliver Anthony’s sperm directly into Heather’s uterus around the time of ovulation.

The first five attempts with intrauterine insemination failed, and Heather and Anthony felt crushed each time. They finally got good news after the sixth try.

In February 2004, they found out that Heather was pregnant and due to have a baby in October. Looking back on it, Heather wishes that they had sought medical help sooner and had known more about infertility. “At the time, I felt like I was the only one with the problem,” she says. But the Panseras’ experience is not uncommon. According to the American Society for Reproductive Medicine (ASRM), 6 million Americans, roughly 10 percent of the population of reproductive age, face infertility.
Here are answers to frequently asked questions about infertility.

Q. What is infertility?

A. Infertility is a disease or condition of the reproductive system that interferes with the ability to conceive. It’s typically defined as not being able to get pregnant after having regular unprotected sex for one year. “Regular” is considered every few days when a woman is ovulating—the time of the month when one or more eggs are released from the ovaries. Couples may want to seek medical treatment sooner than the one-year mark if the woman is over 35 or if there is a history of irregular menstrual cycles or diseases of the reproductive system.

Infertility also includes the inability to carry a pregnancy to term, as in the case of someone who’s had multiple miscarriages, says Diane Clapp, director of medical information at RESOLVE, a nonprofit advocacy organization for men and women facing infertility. “Some people think that infertility is all in the head and can be fixed with relaxation or a vacation,” says Clapp, who is a registered nurse. “But infertility is a medical disease that most people can be treated for.” About two-thirds of people who are treated for infertility will become pregnant, according to RESOLVE.

Q. How is conception achieved?

A. Many people don’t give much thought to the details of conception. But conceiving a baby is the result of a chain of events. One missed step anywhere along the way can throw everything off. First, an egg must be released during ovulation. A man’s sperm must be able to reach the egg and fertilize it. The fertilized egg then must travel through the woman’s fallopian tube to the uterus and be successfully implanted there. For the embryo to develop, the woman must be producing an adequate amount of hormones. For example, human chorionic gonadotropin (HCG) is a hormone that helps maintain a pregnancy. After a fertilized egg is implanted in the uterus, HCG is produced by the developing placenta, the structure that supplies nutrients to the baby.

Sometimes a couple will succeed in conceiving after identifying when the woman ovulates and having sexual intercourse around that time. Using ovulation test kits and basal thermometers can help determine more precisely when ovulation occurs. Basal thermometers can indicate a rise in body temperature, which occurs when a woman ovulates. But infertility is more than just bad timing. It can involve disorders that prevent conception or implantation from taking place.

Q. What are the primary causes of infertility?

A. For men, the primary cause of infertility is a sperm disorder. A man may have no sperm or low sperm, or there could be a problem with how the sperm is moving.

For women, the primary cause of infertility is an ovulation disorder. Normally, a woman ovulates every month, usually around the middle of the menstrual cycle, which averages 28 days. Experts say that women with an ovulation disorder may not ovulate at all or they may ovulate irregularly.

Other common causes of infertility in women are a blockage of the fallopian tubes, which prevents an egg from traveling to the uterus, and hormonal defects that make the uterine lining unprepared for egg implantation or that keep a pregnancy from being maintained.

Q. What are the main risk factors for infertility?

A. A woman’s fertility starts to decrease in her early 30s and takes a big drop after age 35. According to the ASRM, a healthy 30-year-old woman has about a 20 percent chance each month of getting pregnant. By age 40, that chance is only about 5 percent.

Experts say the main reason for the drop is that women are born with all the eggs they will ever have, and the supply of eggs goes down with age. "The quality of the eggs also goes down, which increases the likelihood of miscarriage in older women," says Adelina Emmi, M.D., associate professor of reproductive endocrinology and infertility at the Medical College of Georgia. "You may hear about celebrities having twins at 50, but you don’t always know the details, like whether donor eggs were used."

And though men produce sperm most of their lives and don’t experience the sudden drop in fertility that women do, a man’s fertility may decrease gradually over time. “As men age, their fertility declines later and less dramatically than it does in women,” Emmi says. “There is also evidence that the risk of gene defects in sperm goes up with age.”

The risk of infertility also goes up when either partner has had diseases or surgery that could damage the reproductive organs. For example, a major complication of sexually transmitted diseases for women is pelvic inflammatory disease (PID). This infection can lead to infertility because it causes scarring in the uterus and fallopian tubes. Men may have reproductive
abnormalities due to prostate surgery or a disorder of the testes resulting in a normal sperm production.

"This is an area of medicine where getting a good patient history really counts," Emmi says. "We can pick up all kinds of things that people may not realize affect their fertility—from chronic conditions like prediabetic states and thyroid disorder, which can interfere with ovulation, to blood pressure medication, which can lower a man's sperm count."

Lifestyle risk factors that can impair fertility in men and women include endocrinologists who have completed training in obstetrics and gynecology, followed by specialized training in hormonal problems and infertility. One example of a complex problem is a history of failure to conceive despite regular unprotected intercourse in a woman who has regular menstrual periods and whose male partner has normal sperm. Other examples of complex problems include a woman who has experienced multiple miscarriages or who has severely damaged fallopian tubes requiring the need for treatment with assisted reproductive technologies (ART)—the joining of eggs and sperm in a lab so that fertilization can occur.

The decision about when to ask for a referral to a fertility specialist is a personal one. Experts say that couples should consider the age of the woman, the complexity of their problems, and how they are feeling about the progress of their treatment. Consumers should be proactive about asking their doctors for a referral to a specialist and about investigating the qualifications of the specialist. A certificate of special qualification in reproductive endocrinology and infertility from the American Board of Obstetrics and Gynecology ensures that the specialist has completed a rigorous course of training.

Q. What kinds of doctors evaluate and treat infertility?

A. Obstetrician-gynecologists (OB-GYNs) can evaluate and treat infertility in women. OB-GYNs specialize in general medical care of women, including care related to pregnancy and the reproductive tract. Urologists, who specialize in the urinary tract and the male reproductive organs, can evaluate and treat infertility in men.

More resistant and complex problems are typically handled by "fertility specialists," board-certified reproductive endocrinologists who have completed training in obstetrics and gynecology, followed by specialized training in hormonal problems and infertility. One example of a complex problem is a history of failure to conceive despite regular unprotected intercourse in a woman who has regular menstrual periods and whose male partner has normal sperm. Other examples of complex problems include a woman who has experienced multiple miscarriages or who has severely damaged fallopian tubes requiring the need for treatment with assisted reproductive technologies (ART)—the joining of eggs and sperm in a lab so that fertilization can occur.

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Q. What goes into a fertility evaluation?

A. A standard fertility evaluation includes physical exams and medical and sexual histories of both partners. Men undergo a semen analysis that evaluates sperm count and sperm movement. "We look at the percent that are moving and how they are moving—are the sperm sluggish? Are they wandering?" says Robert G. Brzyski, M.D., Ph.D., associate professor of obstetrics and gynecology at the University of Texas Health Science Center at San Antonio. "Often, it's not possible to identify a specific reason for a sperm disorder," he says. "But there is new recognition that very low sperm or no sperm may be related to genetics—an abnormality of the Y chromosome."

For women, doctors first check to see whether ovulation is occurring. This can be determined and monitored through blood tests that detect hormones, ultrasound examinations of the ovaries, or an ovulation home test kit. "An irregular menstrual pattern would make us suspicious of an ovulation problem, but it's also possible for a woman with regular periods to have an ovulation disorder," Brzyski says.

If a woman is ovulating, doctors then move to a standard test called the hysterosalpingogram, a type of X-ray of the fallopian tubes and uterus. This test involves placing a radiographic dye solution into the uterine cavity. Multiple X-rays are taken. If the fallopian tubes are open, the dye will flow through the tubes and be visible in the abdominal cavity. If the fallopian tubes are blocked, the dye will be retained in the uterus or fallopian tubes, depending on the location of the blockage.

Other tests give doctors more information. For example, ultrasound can be used to examine the female reproductive structures. Hysterosonography is a...
more complicated type of ultrasound that involves putting salt water (saline) into the uterus during an ultrasound exam. “This is more likely to reveal structural abnormalities than regular vaginal sonography will show alone,” Brzyski says. One such abnormality that hysterosonography may identify is fibroid tumors, which may distort the shape of the uterine cavity.

A surgical procedure called laparoscopy also allows doctors to examine structural abnormalities than regular vaginal sonography will show alone,” Brzyski says. One such abnormality that hysterosonography may identify is fibroid tumors, which may distort the shape of the uterine cavity.

FDA Regulation of Human Tissue

The FDA has recently published proposed and final rules to strengthen regulation of human tissue, and expanded the regulations to include human cells, tissues, and cellular and tissue-based products. The new regulations apply to reproductive tissues such as eggs, embryos, and semen.

The rule on registration and listing of the products was finalized on Jan. 19, 2001, and the FDA began requiring various establishments to register with the agency and list the products manufactured starting on March 29, 2004. These establishments include those that recover, process, store, label, package, or distribute the products, or that screen or test donors of them. More than 350 reproductive establishments, including semen banks and fertility clinics, have registered with the FDA.

Reproductive establishments also will be required to comply with donor eligibility requirements, which become effective on May 25, 2005. These requirements establish screening and testing criteria for donors of human cells, tissues, and cellular and tissue-based products to help prevent the transmission of communicable diseases. People who are donating to their own sexual partners are not required to be screened or tested. The regulations do require screening and testing for reproductive product donors who are not sexually intimate partners of people receiving the donation.

FDA experts say that the agency is sensitive to the desire to begin or expand families, and that the regulations are designed to enhance the safety of reproductive tissue, while at the same time recognizing that couples or individuals who know each other should be given the opportunity to make informed decisions about the use of donated reproductive tissue.

the ovaries, uterus, fallopian tubes, and abdominal cavity. This involves inserting a fiber-optic telescope into the abdomen. One advantage of laparoscopy is that it allows doctors to both diagnose and treat conditions such as endometriosis, when uterine cells attach to tissue outside of the uterus. Adhesions, abnormal attachments between two surfaces inside the body, can also be treated in this way.

Doctors have begun to assess the ovarian reserve by measuring hormone levels and seeing how the ovaries respond to various fertility treatments. This helps evaluate the availability of eggs and the likelihood that a healthy pregnancy will result. “Some women who are 35 are fertile while others are not because their supply of eggs is depleted,” Brzyski says. “In the last decade, we’ve learned this can be investigated through a blood test on the third day of the menstrual cycle. If the numbers are normal, it doesn’t guarantee fertility. But if the numbers are abnormal, it points to a serious prob-

infertility is unexplained. This means the reason can’t be identified through diagnostic tests. Even in cases of unexplained infertility, it’s still possible to be treated successfully.

Researchers continue to look for clues that may shed light on unexplained infertility and improve treatment. In 2003, researchers funded by the National Institutes of Health and private sources reported the discovery that an embryo initially attaches to the uterine wall by using specialized molecules located on the surfaces of the embryo and the uterus. The embryo is able to attach because of a sticky interaction with the uterine wall.

The process is “like a tennis ball rolling over a tabletop covered with syrup,” says Susan Fisher, Ph.D., the study’s senior author and an anatomy professor at the University of California, San Francisco. “Understanding the molecular underpinnings of the process that initiates pregnancy is the first step in devising therapies that will improve the rate of implantation.”

Q. What are the conventional treatments for infertility?

A. Conventional therapies, such as drugs or surgery, are used to treat 85 percent to 90 percent of infertility cases. Examples of reproductive surgery for men are vasectomy reversal and varicocele repair, a procedure that may restore fertility by treating varicose veins in the scrotum. Examples of fertility-related surgery for women include removal of noncancerous tumors in the uterus called fibroids, and the removal of endometriosis implants, which can cause infertility.

There are two types of ovulation drug treatments approved by the FDA. Clomid and Serophene (clomiphene citrate) are taken by mouth. Repronex and Pergonal (human gonadotropins) are injected. Both types stimulate the ovaries to produce eggs.

Clomiphene is usually the first line of treatment in women with ovulation problems. “In women who are not ovulating, 60 percent to 85 percent of women will ovulate with clomiphene, and 30 percent to 40 percent will become pregnant,” says Audrey
Gassman, M.D., a medical reviewer in the FDA's Division of Reproductive and Urologic Drug Products. One of the risks of ovulation-inducing drugs is that more than one fetus may result.

Drugs that stimulate ovulation are often used with intrauterine insemination, a procedure in which millions of sperm are inserted into a woman's uterus around the time of ovulation to increase the chance of pregnancy. A partner's sperm or donor sperm may be used.

Q. What are the side effects of fertility drugs?

A. Among the most common bothersome side effects of clomiphene are hot flashes, which occur in 10 percent of women. Abdominal discomfort and bloating is seen in less than 5 percent. Less common are nausea, vomiting, and breast discomfort, which occur in 2 percent of women. Gonadotropins can cause side effects similar to clomiphene. The most common serious adverse event with gonadotropins is ovarian hyperstimulation syndrome. This causes ovarian enlargement and pain and an accumulation of fluid in the abdomen that is potentially dangerous. This results in pain in the pelvic area.

The occurrence of ovarian hyperstimulation syndrome varies with the gonadotropin used, but with most gonadotropins, hyperstimulation occurs in 5 percent to 7 percent of women, with severe cases affecting less than 2 percent of patients, according to Gassman. Mild cases may result in the development of ovarian cysts. "In severe cases of this, patients may need to be hospitalized for lung, kidney, and liver problems, and deaths have been reported, but this is rare," Gassman says. People who experience bothersome side effects while taking fertility drugs should see their doctors.

The incidence of multiple pregnancies with clomiphene is about 8 percent, and the incidence of multiple pregnancies with gonadotropins is up to 20 percent. In contrast, the rate of multiple infant births is 3 percent in the general U.S. population, according to a 2001 report on ART success rates published by the Centers for Disease Control and Prevention (CDC) and the ASRM. Most of the cases of multiple pregnancies due to ovulation-stimulating drugs result in twins, according to the ASRM, but up to 5 percent result in triplets or a higher number of babies. A multiple pregnancy significantly raises the risk of preterm labor, pregnancy complications for the mother, and low birth weight and long-term disability in babies.

Q. Do fertility drugs cause ovarian cancer?

A. Concern over a link between fertility drugs and ovarian cancer came from
studies published in the early 1990s that suggested the risk of ovarian cancer might be significantly increased in women exposed to ovulation drugs. "But more recent studies have failed to corroborate a strong association between fertility drugs and ovarian cancer in the general population," Gassman says.

One study, supported by the National Cancer Institute, evaluated more than 12,000 women and did not find a strong link between ovulation-stimulating drugs (clomiphene and gonadotropins) and ovarian cancer. The researchers also concluded that slight but non-significant elevations in risk with drug use among certain subgroups support the need to continue monitoring long-term risks. The study was published in the June 2004 issue of Obstetrics and Gynecology, the journal of the American College of Obstetricians and Gynecologists.

Gassman says, "The FDA continues to monitor adverse events possibly associated with these drugs and takes appropriate action when necessary based on our current understanding of the risks and benefits."

Q. What is the role of assisted reproductive technology?

A. ART is used when conventional treatment has failed or when no other treatment is available, such as when the woman's tubes cannot be repaired or the man's sperm count is very low. In vitro fertilization and embryo transfer (IVF-ET) accounts for 98 percent of ART procedures, according to the CDC.

Amy Stewart, 29, a nursing home administrator in Warrenton, Ga., turned to in vitro fertilization after exhausting other options. She was diagnosed with endometriosis in 2000 and became pregnant in 2001 after taking fertility drugs. But her pregnancy was ectopic, a dangerous condition in which the fertilized egg implants outside of the uterus, usually in the fallopian tubes. Surgery to treat the ectopic pregnancy resulted in further scarring of her fallopian tubes. She later took fertility drugs in preparation for intrauterine insemination (IUI), and had three unsuccessful IUI attempts. On the fourth IUI attempt, the procedure was canceled because the prognosis for success was poor.

To begin the IVF process, Stewart took fertility drugs to stimulate her ovaries to produce many eggs. In March 2003, her eggs were retrieved and put in a dish with her husband's sperm. About 24 hours later, they were checked to see if fertilization had taken place. It had, and the resulting embryo was transferred directly into her uterus, bypassing the fallopian tubes. Stewart found out she was pregnant on March 19, 2003, and had a baby boy in November 2003. In vitro fertilization can also be performed with donor eggs or donor sperm.

According to the CDC, in 2001, 40 percent of ART procedures that progressed to the "transfer" stage resulted in pregnancy, and 33 percent resulted in live-birth deliveries. "Transfer" refers to transfer of the embryo from an incubation vessel to the uterus. Data were collected from 385 U.S. medical centers by the Society for Assisted Reproductive Technology, an affiliate of the ASRM.

As a result of ART procedures conducted in 2001, the CDC reported that there were 29,344 live-birth deliveries and 40,687 infants total. The difference in the number of deliveries compared to infants born is due to multiple pregnancies. People who use ART are more likely to have multiple births than those who conceive naturally. This risk should be discussed with a doctor. The number of pregnancies resulting in triplets or a higher number of babies has decreased since 1999, when the ASRM updated guidelines on the number of embryos that should be transferred into the uterus.

According to the ASRM, the average cost of an IVF cycle is $12,400. Health insurance coverage for infertility depends on where consumers live and the type of services needed. As of September 2004, the following 14 states
required insurers to cover some form of infertility treatment: Arkansas, California, Connecticut, Hawaii, Illinois, Maryland, Massachusetts, Montana, New Jersey, New York, Ohio, Rhode Island, Texas, and West Virginia.

Q. What other types of ART are being used?

A. IVF is the most common type of ART and there are other variations on the basic procedure, some of which remain controversial. People should learn about both the benefits and risks of any medical procedure.

Q. How can a couple deal with the emotional impact of infertility?

A. Kevin Carton, 40, of Vienna, Va., and his wife Sheryl, 38, sought counseling soon after they were diagnosed with infertility in 1994. A fertility evaluation revealed that Kevin produced no sperm. Kevin and his wife ultimately chose donor insemination, a process in which donor sperm was put into Sheryl’s uterus. They now have three children.

“The whole process is a series of decisions,” Garton says, “and it can be excruciating trying to figure things out.” They obtained a referral to a psychiatrist who specializes in infertility. “We focused on coping and talking about why this happened to us and how we felt about it,” he says. “I initially took the news very hard and felt that I had let my wife down, and I found out that she saw it as more of a joint issue.” They also talked through treatment options with the psychiatrist.

Garton has been an active member of RESOLVE and feels that the support system has been critical in helping him and his wife deal with infertility. “People don’t mean to say insensitive things, but when a couple says something like they accidentally got pregnant, it just crushes a person with infertility,” Garton says. “It’s important to have a group of people to talk with who are going through the same thing you are.”

After they chose donor insemination, they had to deal with a range of issues, from how to choose a donor to how to discuss it with family, friends, and the children. “What it came down to for us,” Garton says, “is that whether you conceive naturally, get medical treatment, or adopt, your kids are your kids. When you are diagnosed with infertility, you think you’re different in some way at first. But I’m just a regular person who wanted to make a family.”

‘... Whether you conceive naturally, get medical treatment, or adopt, your kids are your kids.’
The anthrax attacks in the fall of 2001 shocked the nation and killed five people. In all, the Centers for Disease Control and Prevention (CDC) reported 22 cases of bioterrorism-related anthrax in 2001, mostly in employees of the U.S. Postal Service and news outlets. Half of the people had cutaneous (skin) anthrax and half had inhalational (lung) anthrax, the deadliest form.

Before this time, there had been only 18 other cases of inhalational anthrax during the 20th century, according to the CDC. The last had occurred in 1976. Most of those cases affected textile mill workers who were exposed to goat hair, wool, and other animal products infected with the spore-forming bacterium Bacillus anthracis.

At the time of the 2001 attacks, the Food and Drug Administration had approved three types of antibiotics to prevent or treat anthrax: Cipro (ciprofloxacin), drugs in the tetracycline class such as doxycycline, and some drugs in the penicillin class such as procaine penicillin G. Most of those diagnosed with anthrax were treated with antibiotics, and more than 10,000 people took them as a precautionary measure, according to the CDC. The incident heightened awareness of the need to improve the preparedness for dealing with bioterrorist attacks in the United States.

Building Up Countermeasures

Since then, federal agencies have strengthened partnerships to develop and improve medical countermeasures—human and animal drugs, vaccines and other biologics, blood and blood products, diagnostic tests, and devices that can prevent, diagnose, and treat illnesses related to a terrorist attack. The cornerstone of this effort is the Project BioShield Act, which President Bush signed into law in July 2004.

Project BioShield establishes a permanent funding source through which the federal government can buy medical countermeasures from private companies. The fiscal year 2004 appropriation for the Department of Homeland Security includes close to $6 billion over 10 years for buying “next-generation” countermeasures against anthrax, smallpox, and other infectious agents, as well as antidotes against chemical and radiological threats. This encourages researchers to improve medical products that have stayed the same over the last few decades. The currently licensed smallpox vaccine, for example, is the same as what was used during the 1960s.

Health and Human Services Secretary Tommy G. Thompson and Homeland Security Secretary Tom Ridge oversee Project BioShield. "This law is a clear signal that the U.S. government is prepared to be a full partner with the research community in the fight against bioterrorism," Thompson says. "From our research scientists at NIH to the pharmaceutical staff at FDA, we are moving forward, and now with Project BioShield, we will be able to better protect the health and safety of all Americans.”

The administration already has begun to acquire various countermeasures, including new smallpox vaccines, new anthrax vaccines that will be stockpiled in 2005, new anthrax treatments that are intended to neutralize anthrax toxins, and an antitoxin for botulinum toxin. This adds to the Strategic National Stockpile (SNS), which is intended for use in response to national emergencies. The SNS is a stockpile of antibiotics, antitoxins, vaccines, medical supplies, medications, and surgical items. The stockpile now has more antibiotics to treat anthrax than ever before and more treatments for radiation poisoning, chemical agent exposure, and other biological pathogens. And there is now enough smallpox vaccine for every person in the United States—286 million doses.

Research and Development

Project BioShield also provides more money to support research and development on medical countermeasures through the National Institutes of Health (NIH). The National Institute of Allergy and Infectious Diseases (NIAID) is the main institute supporting biodefense research. The NIAID will have more authority to award contracts and research grants to develop medical countermeasures against biological, radiological, or nuclear attack. The grant process for biodefense medical research normally takes up to two
years. HHS estimates the process under Project BioShield will take roughly six months.

Using the CDC's listing of biological agents that pose the greatest threats to the public health, the FDA works with the NIH, the CDC, and other HHS agencies to identify the need for better treatments. The highest priority is on agents labeled by the CDC as "Category A," which include the organisms that cause anthrax, plague, smallpox, tularemia, viral hemorrhagic fevers, and botulism.

"We've encouraged manufacturers to come to us for early-stage meetings to see if we can help focus studies that accelerate product development," says Cynthia Kelley, senior adviser for counterterrorism/medical countermeasures in the FDA's Center for Biologies Evaluation and Research (CBER). "CBER researchers are also working to develop new and improved methods to evaluate the safety, purity, and potency of biological products needed in the fight against terrorism."

The FDA, the NIH, and HHS recently collaborated on two workshops on improving medical countermeasures. A workshop in June 2004 focused on strategies for developing anthrax treatments. Another workshop in October 2004 explored the use of animal models that may be most appropriate for evaluating new plague vaccines, as well as which immune responses may indicate protection against plague.

**Emergency Use Authorization**

Project BioShield gives the FDA authority to make promising drugs, biologics, diagnostics, or devices quickly available in emergencies. The FDA will interpret safety and effectiveness information by considering a product's stage of development, available scientific data, whether the product is approved for another use, the seriousness of the clinical condition, specific circumstances of the emergency, and whether alternative treatments are available.

"In the traditional drug development setting, FDA considers a product investigational until it is found to be safe and effective in the formal review process," says Brad Leissa, M.D., deputy director of the FDA's Division of Counter-Terrorism in the Center for Drug Evaluation and Research. "However, with the advent of the emergency use authorization, an investigational medical countermeasure might effectively be deployed to save lives during a public health emergency. From a logistical and operational standpoint, this new authority assures that we can respond more efficiently to a terrorist attack."

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**For More Information**

Project BioShield

[www.whitehouse.gov/bioshield/](http://www.whitehouse.gov/bioshield/)
Take the FDA Consumer QUIZ

According to public health officials, which groups of people should be sure to get a flu vaccination this season? At what age does a woman’s fertility begin to decrease? Does eating too much sugar cause attention-deficit hyperactivity disorder? To find out how much you know about these and other health-related topics, take our quiz.

Hint: The answers to all of these questions can be found in the November-December 2004 issue of FDA Consumer (and at the bottom of this page). Good Luck!

1. Scientific evidence shows that attention-deficit hyperactivity disorder is caused by:
   a. poor parenting
   b. high sugar intake
   c. consuming food additives
   d. excessive TV viewing
   e. none of the above

2. The cure for attention-deficit hyperactivity disorder is:
   a. FDA-approved medications
   b. behavioral therapy
   c. a combination of a and b
   d. brain surgery
   e. There is no cure, but medications and behavioral therapy can help treat the symptoms

3. Children who take a prescribed dose of a stimulant to treat attention-deficit hyperactivity disorder:
   a. eventually become addicted
   b. have no side effects at all
   c. may grow at a slower pace
   d. have an increased appetite

4. A person with deep vein thrombosis
   a. may have swelling in the leg
   b. may have pain in the leg
   c. may not notice any signs of it
   d. none of the above
   e. all of the above

5. How many Americans face infertility?
   a. 2 million
   b. 4 million
   c. 6 million
   d. 8 million

6. At what age does a woman’s fertility start to decrease?
   a. mid 20s
   b. early 30s
   c. late 30s
   d. early 40s

7. Which of the following are risks of taking fertility drugs?
   a. hot flashes
   b. development of ovarian cysts
   c. multiple pregnancies
   d. abdominal discomfort
   e. all of the above

8. When the FDA plans to issue a new regulation or revise an existing one, it places an announcement in the:
   a. Code of Federal Regulations
   b. FDA Almanac
   c. Federal Register
   d. FDA Consumer

9. Certain groups that are at higher risk for flu complications should get flu shots first this season. Which of these groups is not in the high-risk category?
   a. people over 65
   b. school teachers
   c. babies 6 months to 23 months
   d. health care workers

10. What is the main federal agency supporting biodefense research in the United States?
    a. the Food and Drug Administration
    b. the Centers for Disease Control and Prevention
    c. the National Institute of Allergy and Infectious Diseases
    d. the National Institute of Environmental Health Sciences

Answers
What’s Your Cholesterol IQ?

Many of us may remember the dreaded “pop quiz” from school and how it sometimes created that sinking feeling of being unprepared. Well, the National Institutes of Health has its own pop quiz it would like you to take. You may not be prepared for it either, but the quiz answers could help save your life.

The quiz asks 11 true-false questions and then allows you to gauge your performance—your cholesterol IQ—as you read detailed answers to each of the questions. Even if you miss some of the quiz questions, you’ll be ahead of the game if you read and heed the correct answers, which cover subjects such as heart disease in women, fish oil supplements, and food labels. Take the quiz at www.nhlbi.nih.gov/health/public/heart/chol/chol_iq.htm.

Also regarding cholesterol, the NIH has created an online calculator that tells you—based on cholesterol numbers, blood pressure, age, and other factors—your probability of having a heart attack over 10 years. The calculator is designed for adults older than 20 who do not have heart disease or diabetes. It can be found at http://hin.nhlbi.nih.gov/atpiii/calculator.asp.

View Your Local Environment Through This ‘Window’

Ever wonder about air and water quality in your local area? How about issues such as fish advisories or the conditions of watersheds in your region? There’s an easy way for you to find this information quickly. You simply take a peek into the Window to My Environment, a Web site of the U.S. Environmental Protection Agency.

Here’s how it works. Go to the site and type in your ZIP code or city and state in the box provided. This creates your “window,” which is a map of your region into which you can place dozens of indicators. For example, if you are interested in where hazardous waste or toxic release areas are, you simply click those boxes, and the map displays the known spots, which are color-coded for easy identification on the map. The site also lets you find where churches, schools, hospitals, and other features are located.

If you want even more detail on your local conditions, the site can answer specific questions such as what facilities in your region release emissions into the air or if there are any polluted waters. For each region displayed, you also can find out what is being done—tracking, restoring and protecting—to aid the environment in that area.

To look through the “window,” go to www.epa.gov/enviro/wme.

Food Tampering: Caution Can Pay Off

Though the deliberate tampering of food to cause disease is rare in the United States, the FDA is enhancing its surveillance of foodborne disease and bolstering inspections of domestic and foreign food-producing plants.

As a consumer, you also can play a role by following a list of tips on an FDA Web site called Food Tampering: An Extra Ounce of Caution. The site covers measures you can take at home and at the grocery store, and it advises what to do if you suspect product tampering.

Check out the tips at www.cfsan.fda.gov/~dms/fstamper.html.

John Henkel is a member of the FDA’s Website Management Staff.
Learning to Thrive With ADHD

By Toni Wood

"Baggeldaggit!"
My husband looked at me, then at our 2-year-old son, Jason, not understanding what he was saying. We had learned that when Jason became frustrated, we needed to figure it out quickly ... or else.

"Baggeldaggit!" He said it again.
This was his third time, and he was getting insistent. Frustrated ourselves, we called in our older son to help solve Jason's mystery. With demonstrative help from Jason, we finally determined that "Baggeldaggit" meant "Inspector Gadget," Jason's favorite TV show.

In addition to language, Jason later struggled with
• handwriting legibility
• inability to stay focused and sit still in class
• poor short-term memory resulting in forgotten assignments
• inability to process multiple instructions.
Some of these challenges, plus Jason's inability to adhere to school rules, contributed to his expulsion from Montessori preschool.

Eventually we discovered that many of Jason's impairing challenges were part of undiagnosed attention-deficit hyperactivity disorder (ADHD), along with difficulty writing (dysgraphia) and learning disabilities. Once diagnosed, he was prescribed medication and therapy to help manage many of these challenges. The diagnosis provided an explanation, but we still faced an uphill battle; each year we had to educate new teachers who were intent on "fixing" Jason.

In 1996, when Jason was 10, I discovered that "the apple does not fall too far from the tree." Feeling overwhelmed and exhausted, I sought professional help that led to my own diagnosis of ADHD and depression. Put on medication and receiving therapy, I soon learned to manage my ADHD, and I put the depression behind me.

In hindsight, I recognize many symptoms of ADHD in my past. I remember always feeling pressured and overwhelmed by daily tasks. Bills were piled up all over the house, the phone was constantly ringing with collectors demanding to be paid, the house could pass for an out-of-control yard sale, and laundry rarely got folded, let alone put away. I was supposed to be modeling good values and principles for my kids—how could I be a model for them when I couldn't do it myself?

Having watched Jason's frustration with school motivated me to find ways to help him and others who also struggled. I knew what it was to struggle with ADHD; the road to my first college degree was long and hard and filled with many potholes.

For me, college was a never-ending cycle of constant stress. I was always anxious about taking notes and recording every word my professors said, worried I would miss something important. Distractions were everywhere. College education was a living torture. Despite all the stress, I still managed to graduate. My husband teases me about taking two kids, three states, and four colleges to get my degree. That's true, but somehow I managed—and with honors.

Eventually I went back to pursue another degree, this time in psychology. I had gained experience developing and testing successful strategies that supported my unique way of learning. I discovered how my mind wandered, which contributed to my inability to focus. I also discovered how perpetual motion helped me focus, and tapping a pencil or jiggling my feet was calming.

My new strategies, coupled with the college disabilities services office plan to provide note-taking support and additional time to complete exams, were key components that had been missing in my past.

Armed with experience and an array of effective tools, I received my second degree in less than two years. Not finding post-graduate programs that suited my interests, I searched for alternatives. I wasn't sure what I was looking for until I met an "ADD coach." I had found my new career! A few months later, I discovered the path that would get me there. I enrolled, and eventually graduated, at the ADD Coach Academy, a yearlong comprehensive coach-training program where I learned the skills to powerfully coach individuals with ADHD.

My coaching practice focuses on college students and newly diagnosed adults with ADHD. Because of my own experiences, I want to help others understand that ADHD does not have to be a constant struggle. It is through the struggle that we learn our lessons of success. I want to share my story so others won't have to go through unnecessary pain.

ADHD can be a challenge or a catalyst. With support from people who understand ADHD, the wounds of the past can become the present catalyst of wisdom that motivates individuals to create success right now.

Toni Wood is an ADHD coach certified by the ADD Coach Academy with a nationwide practice. She lives in Chesapeake, Va.
We’re protecting America’s health.

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