An *FDA Consumer* Special Report

Your Guide To

WOMEN'S HEALTH

Third Edition

FDA on the Internet: **http://www.fda.gov/**

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Your Guide To
Women's Health

Third Edition

September 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Dear Reader:

This *FDA Consumer Special Report* addresses a subject that is one of our top priorities: women's health. Please read it carefully and share it with others.

We at the FDA are involved in a wide range of health issues that affect women of all ages. The subjects are as varied as the participation of women in clinical trials for new drugs; the spread of STDs; the prevention, diagnosis and treatment of breast cancer; the choice of contraceptives; and information on menopause and osteoporosis.

This agency is committed to providing women with reliable health facts, and to ensuring that medications, medical devices, cosmetics, and other FDA-regulated products are safe and effective for everyone. The FDA's Office of Women's Health seeks to focus appropriate FDA attention on women's health issues and concerns. Additionally, we realize that women are often so busy juggling work and family obligations that they may not take time to care for themselves. The Office of Women's Health has designed a new educational outreach program called *Women's Health: Take Time to Care,* aimed at helping women take better care of themselves through informed use of medicines, health screenings, and the food label. We believe that widespread awareness of the hazards and problems to be avoided and knowledge of the remedies that are available if prevention fails are among the best contributions to the public health.

This special report is dedicated to contributing to increased awareness of women's health issues. We invite you to join with us as we work together to enhance consumers' understanding of the role they can play in protecting their own health.

Sharon Smith Holston

Sharon Smith Holston
Deputy Commissioner for External Affairs

Introduction

by Donna E. Shalala, Ph.D.
Secretary of Health and Human Services

Someone once said, "If you educate a woman, you educate a family." Yet, while women have always addressed the health needs of family members, too often they ignore their own needs. This FDA special report on women's health will help give you the information you need to take care of yourself.

This book is for all women. And, it is about the twin keys to good health: prevention and early detection. It is far less costly, and less painful, to prevent disease than to treat it. Of the 2 million deaths that occur each year in the United States, about half are preventable. While women generally live longer than men, too many women die prematurely from tragedies like lung cancer and heart disease.

Don't become a statistic. By taking personal responsibility for your health, you can prevent injuries and many debilitating diseases. How? By getting regular check-ups and preventive screenings. And, by incorporating some relatively simple tasks into your daily life—like physical activity and good nutrition—you can head off danger, instead of gambling with risks. Here are a few important reminders:

Stay tobacco-free. Smoking is the number one preventable cause of death among American women. In fact, more than 140,000 women die each year from tobacco-related illnesses. Staying away from tobacco can drastically reduce your chances of cancer, heart disease, stroke, and a number of other chronic health problems. If you don't smoke, don't start. If you do, stop right now—it's never too late to quit.

Fight breast cancer. About 44,000 women die from breast cancer each year, but with early detection you can find cancerous lumps before diseased cells spread. That can sometimes make the difference between life and death. So get regular clinical exams. Examine your breasts every month. And get regular mammograms. Talk to your doctor about when to start. Remember, mammograms begin at 40. And, if you are enrolled in Medicare, it will help pay for your mammogram. For more information about breast cancer and the names and locations of FDA-certified mammogram facilities, call (1-800) 4-CANCER.

Protect yourself from STDs. The Centers for Disease Control and Prevention recently reported that women account for an increasing percentage of newly reported AIDS cases. Take every precaution against AIDS and other sexually transmitted diseases. Sexually transmitted diseases often show no symptoms in women and can lead to infertility or cervical cancer. So get regular pap tests and ask your doctor if you should be tested for STDs.

Eat right. Eating right doesn't mean starving yourself. It means eating a balanced diet high in grains, vegetables and fruits and low in fat and cholesterol. And, it means getting enough calcium to prevent osteoporosis—a crippling disease that makes brittle bones susceptible to fractures. Read the food labels and make good nutrition a lifelong habit. It can improve your health and reduce your chances of premature death from heart disease, stroke and some cancers.

Get active. Stay active. Take time out from your daily routine to get active. It can improve your heart, lungs, weight, and mental health. *Physical Activity and Health: A Report of the Surgeon General* recommends regular moderate physical activity for 30 minutes a day at least five days a week. That means you don't have to train like an Olympic athlete to enjoy the benefits of a healthy lifestyle. Walking, bicycling, or even gardening for 30 minutes, most days of the week can save your health and maybe even your life.

Use medicine wisely. Up to 50 percent of people who take medicines don't use them as directed. And that takes a toll on our nation's health and costs us about $20 billion each year. So follow your medication instructions carefully. Keep track of all of the medications you are taking. And if you have any questions, ask your doctor or pharmacist for help.

My last piece of advice is: Read this book. Use this book. Pass it on to your friends. Discuss it with your friends and health providers. And feel secure in knowing you've taken effective steps to live a long and healthy life.

Office Of Women's Health

by Isadora Stehlin

When FDA's Office of Women's Health announced that 1995 annual funds were available for agency research projects, Mary Lou Tortorello, a microbiologist with FDA's Center for Food Safety and Applied Nutrition, knew just the project to propose. She wanted to develop a rapid test for *Listeria monocytogenes*, a microorganism widespread in the environment that may contaminate many types of foods. She thought the test could have a major impact on women's health, since *Listeria* can cause miscarriages and stillbirths in pregnant women.

"By current standard methods, it takes at least four days to detect *Listeria* in food, and that's only if everything works as it is supposed to," says Tortorello. "A rapid test could really enhance food safety."

Tortorello's research is one of more than 50 projects within the agency that have been funded by the Office of Women's Health since it was established in July 1994.

The office, with a $2 million annual budget, promotes testing of FDA-regulated products in women, supports research and education to increase knowledge of women's health issues, and forms partnerships with other government agencies and advocacy groups to advance women's health objectives.

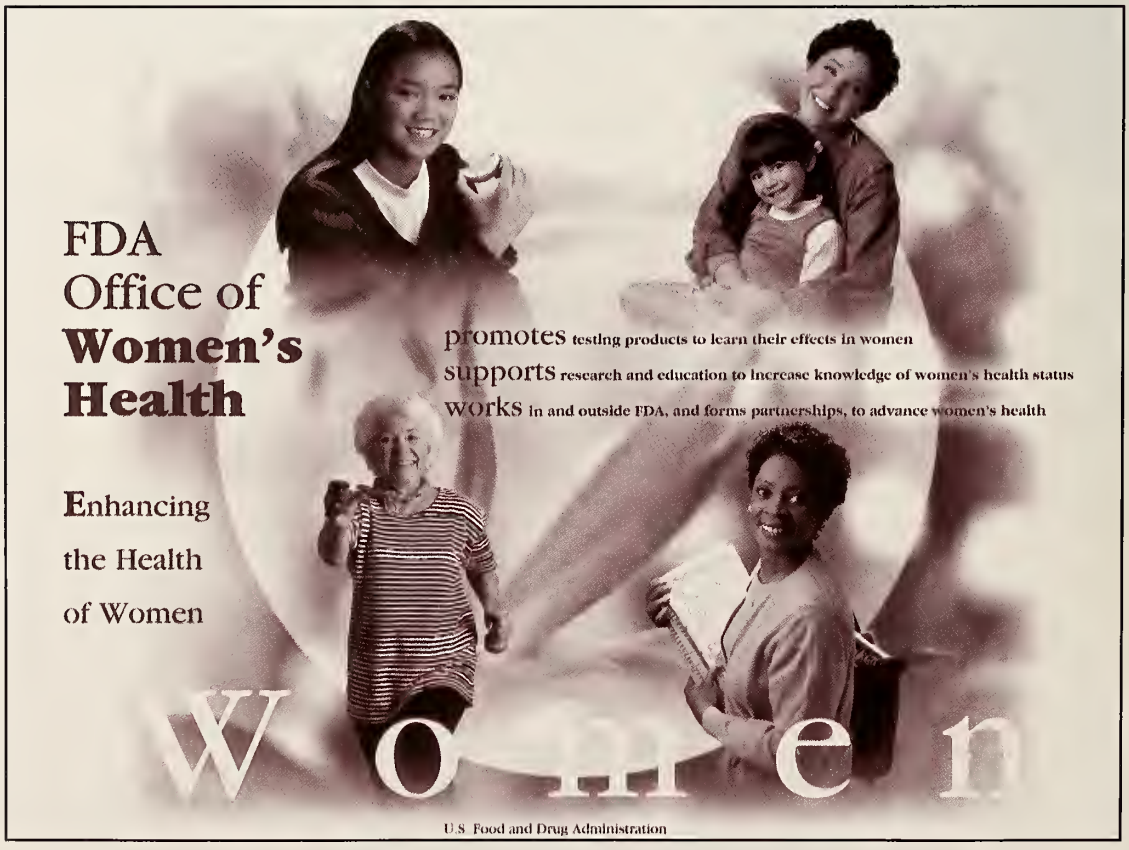
Women's health issues of particular concern to OWH include:

- cardiovascular disease
- cancer screening and treatment
- sexually transmitted diseases, including HIV
- contraception, pregnancy and childbirth
- hormone replacement therapy for menopause
- osteoporosis and other diseases affecting older women
- autoimmune diseases.

Central to the office's mission are increasing the number of women in clinical trials and analyzing data for important effects that vary with gender.

Historically, women have been neglected in clinical trials for new drugs, devices, and biological products. Attention to remedying this situation was integral to the genesis of the Office of Women's Health and is one of its major issues, explains Audrey Sheppard, acting director of the office.

One of the first projects the office funded in 1994 was a study to determine how women newly diagnosed with breast cancer obtained clinical trial information. "There's a great misunderstanding about the National Cancer Institute's Physician Data Query [PDQ] clinical trial database," says Patty Delaney, project coordinator and cancer liaison in FDA's Office of AIDS and Special Health Issues. Not every trial is included, she explains, only trials sponsored by NCI and a few others submitted voluntarily by nongovernment sponsors. "If a manufacturer is conducting one on its own, it is likely not to be in NCI's database."



The original of this artwork, a full-color 8-by-10-foot portable stand-alone display produced by FDA's Communications Staff, is part of an exhibit the Office of Women's Health uses to educate the public at health fairs, workshops, and other events.

The project, conducted by a contractor for FDA, involved calling more than 100 different telephone numbers that supplied cancer information. Results showed there was no simple, comprehensive way to find out about all the current clinical trials on breast cancer. University medical centers and other research sites often only offered information on studies they were conducting, and when asked where someone could get information on other studies, callers were usually referred to NCI's cancer hot line, (1-800) 4-CANCER.

Because there is no centralized source for information on all current clinical trials, "patients and their doctors have trouble finding suitable trials, and manufacturers have trouble filling trials," says Marietta Anthony, Ph.D., a microbiologist with the Office of Women's Health.

Based on these conclusions, the National Action Plan on Breast Cancer, an organization funded by both private groups and the Department of Health and Human Services, awarded FDA $100,000 to assist NCI in getting drug, biologics and device manufacturers to voluntarily add their breast cancer clinical trials to the PDQ database.

The office has also funded research projects and studies to:

- Develop a computer model to simulate the potential for a virus to break through a protective barrier such as latex, used in surgical gloves and condoms.
- Develop a pilot tracking system to monitor the participation of women in clinical trials.
- Examine the effects of the anti-breast cancer drug tamoxifen (marketed as Nolvadex) on the rat uterus. Preliminary studies of women taking tamoxifen, which can delay or prevent relapse in patients who have undergone surgery for breast cancer, have shown that the drug poses an increased risk of cancer of the uterus.
- Determine if changes in female sex hormone levels that occur during the menstrual cycle, pregnancy and menopause affect the activities of cytokines (hormone-like proteins that act as communicators between cells). Limited evidence suggests that the cause of systemic lupus erythematosus, an immune-system disease that mainly affects women, may be linked to the interaction of these cells.

In addition to funding research, the office has also supported education projects that address women's health issues. One of these efforts, "The Minority Women's Health Empowerment Project," attracted nearly 500 participants. Theresa Holmes, a public affairs specialist with FDA's Philadelphia office, and Joan Lytle, a public affairs specialist with the agency's Newark office, developed the project and six half-day workshops held during the fall of 1995. Four were held in different New Jersey cities, one in Philadelphia, and one in Wilmington, Del.

"These workshops provided really practical nuts and bolts information on diseases and conditions, prevention and diagnosis, and remedies," says Sheppard.

Some critical health problems of minority women include cervical cancer, which is approximately three times higher among black women than white women; heart disease, which is the leading cause of death in Latino women; and hypertension, stroke, diabetes, lupus, and other chronic diseases, which are responsible for a disproportionate number of deaths in young African-American women.

Other education projects funded by the Office of Women's Health include:

- Mammography Quality Standards Act brochure for consumers
- Mammography Quality Standards Act speakers kit to help FDA and state radiation control personnel explain MQSA requirements, as well as FDA's programs and policies for mammography facility accreditation and inspection
- Women of Color Outreach project to expand minority women's involvement in the FDA policy development process
- Hispanic Women's Health Conference in Miami on May 9 and 10, 1996
- Asian Pacific Islander Group outreach to encourage use of screening tests such as mammograms and pap smears. Asian language translations of FDA educational materials were distributed at health conferences, community activities, and medical centers in California.
- Women's Health Internet Initiative to provide information about women's health issues related to food safety, nutrition and cosmetics. The World Wide Web address for this site is *http://vm.cfsan.fda.gov/~dms/wh-toc.html.* In addition, OWH has expanded its Internet availability by establishing its own home page at *http://www.fda.gov/womens/.*

OWH also coordinates working groups that bring together agency experts. For example, for the working group on older women's issues, "the office is bringing together people throughout the agency who have a piece of the osteoporosis puzzle—the people who approve the drugs, the people who approve the bone measurement devices, and the people who know about calcium and other foods," explains Sheppard.

OWH is implementing a public health education program, "Women's Health: Take Time To Care," on which it embarked in the spring of 1996. The program's purpose is to encourage women to take time out of their busy lives to practice healthful living: to eat smart, get screenings (such as mammograms and pap smears) and take medications wisely. (The medications message is receiving the initial publicity, with the others to follow.)

These are the areas in which a woman's efforts can result in better health outcomes; they are also areas where FDA has responsibility for regulating the products and wants to see those products used to best advantage. For example, older women may take a large number of prescription and nonprescription medications. Mistakes taking them can lead to unnecessary illness and even death.

The program initially is focusing on women 50 years and older, particularly in underserved populations. It may be expanded to deliver other messages in the future. Printed materials such as brochures and posters are being produced, as are kits for bringing these messages to communities around the country.

As the Office of Women's Health continues to define its role, "we really do see ourselves as not just coordinating and educating," says Sheppard, "but also determining where there needs to be advances in thinking, in policy, and in regulation." ■

Isadora Stehlin is a member of FDA's public affairs staff.

Progress Against Breast Cancer

by Marian Segal and Judith Levine Willis

More than 20 years ago, Joyce Fine of Bethesda, Md., had a radical mastectomy to treat breast cancer. She didn't discuss her disease much with anyone then, except her husband.

In those days, Fine remembers, cancer was not talked about. "Everything was secretive then. Obituaries of people with cancer read that they died of 'a lingering illness'." Fine thinks that her father's mother may have had breast cancer, but she's not sure. The impression came from a single conversation she happened to overhear.

A New Attitude

Today people are not only open and truthful but often also activist about breast cancer. Along with strides in diagnosis and treatment have come long overdue changes in attitudes and awareness about the disease. Betty Ford, Nancy Reagan, Happy Rockefeller, Shirley Temple Black, Gloria Steinem, and many other public figures have come forward in recent years to tell about their experiences. But it's certainly not just because of the celebrities that breast cancer has captured the public's attention.

According to the American Cancer Society, breast cancer yearly strikes about 185,000 women and kills about 44,000. It is second only to lung cancer in cancer deaths in women. According to the National Cancer Institute (NCI) the disease

strikes 1 in 8 American women (1 in 9 before age 85), so it's unusual *not* to know someone who has had breast cancer.

Yet progress is being made. In March 1997, NCI announced that for the first time since scientists began keeping cancer statistics in the 1930s, deaths from breast cancer had declined—by 6.3 percent from 1991 through 1995. This is part of an overall trend of decreasing cancer deaths.

Though the average lifetime risk of breast cancer for a woman is 1 in 8, a woman's risk of getting it in any given year is less than 1 in 100. A woman's risk rises continuously with age. According to NCI, on the average, a woman's risk of getting breast cancer is about: 1 in 19,600 by age 25; 1 in 2,500 by age 30; 1 in 200 by age 40; 1 in 50 by age 50; 1 in 24 by age 60; 1 in 14 by age 70; 1 in 10 by age 80; and by age 85, 1 in 9.

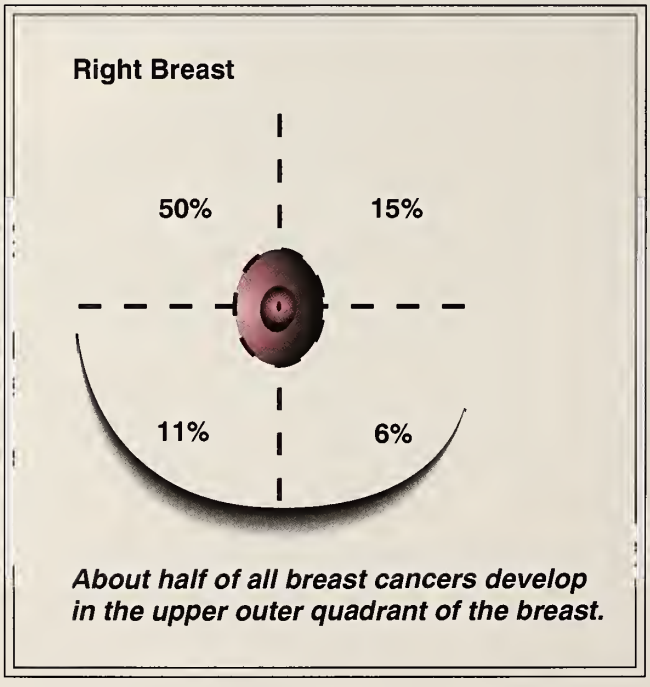
Women whose mothers or sisters have had breast cancer have two to three times the usual risk of developing the disease. The risk is greatest if the relative developed breast cancer before menopause or if both breasts were involved. Nevertheless, hereditary breast cancer accounts for only 5 to 10 percent of breast cancer cases. As NCI researcher Susan Bates, M.D., says, the statement, "There's no breast cancer in my family" should provide a woman no security whatsoever.

Overall, breast cancer is more common in white women from North America and Northern Europe and in women of high socioeconomic status. However, African American women under 50 have a higher risk than white women of this age, while after age 50, the breast cancer risk of African American women is lower than for white women. Women of Eastern European (Ashkenazi) Jewish descent appear to be at higher risk than other groups due to genetic factors.

BRCA Genes

Alteration of a gene scientists named BRCA1 (for Breast Cancer 1) has been linked to the development of inherited breast cancer, as first reported in the Oct. 7, 1994, issue of the journal *Science*. The research was accomplished by the scientists of Myriad Genetics, Inc., the University of Utah, and the National Institutes of Health. This gene, located on chromosome 17, is one of several genes that, when normal, suppress the growth of tumors. BRCA1 has also been linked to familial ovarian cancer (see "Ovarian Cancer," page 111).

It has been estimated that women with a mutated BRCA1 gene may have a lifetime breast cancer risk of up to 85 percent (compared with about 12 percent for women in general). However, a report by Jeffrey P Struewing, M.D., and colleagues in the May 15, 1997, *New England Journal of Medicine,* indicates that the risk may be overestimated. In any case, it is important to note that not all women who have the BRCA1 alteration will develop breast cancer. The altered gene does not seem to increase breast cancer risk in men.



About half of all breast cancers develop in the upper outer quadrant of the breast.

In the general U.S. population, this mutation occurs in 1 in 300 to 1 in 800 women. But it occurs in 1 of 10 Ashkenazi Jewish women. Two specific BRCA1 mutations have been identified in several families of Jewish Ashkenazi descent with a family history of breast cancer. The mutations are named 185delAG and 5382insC. In addition, NIH scientists reported in the Oct. 1, 1995, issue of *Nature Genetics* that mutation 185delAG had been found in blood samples of 1 percent (8 of 858) of Ashkenazi Jews whose family or personal cancer history was unknown. None of 815 blood samples of individuals not selected for ethnicity had this alteration.

NIH scientists are conducting follow-up studies of 3,000 to 5,000 people in the Washington, D.C., and Long Island, N.Y., Ashkenazi Jewish populations to see how the presence of this alteration correlates with cases of breast and ovarian cancer.

The alteration of a second gene, BRCA2, located on chromosome 13, is also linked to inherited breast cancer. This link was identified and first reported by researchers at Duke University and the United Kingdom's Institute for Cancer Research in the Dec. 21, 1996, issue of the journal *Nature*.

"BRCA1 seems to be responsible for about half of inherited breast cancers,"

Mammography: A Lifesaving Step

Mammography can be lifesaving. It is widely agreed that women 50 and over should have a mammogram yearly. Widespread mammography screening programs for women in this age group can reduce breast cancer death rates by 30 percent, according to a seven major randomized controlled clinical trials. This is especially important for older women, since the incidence of breast cancer increases dramatically with age.

Mammography is the best method available for detecting tumors in their early stages. It help can detect 85 to 90 percent of breast cancers in women over 50 and can discover a tumor up to two years before a doctor or patient would otherwise know it was there.

For women aged 40 to 49, the following recommendations had recently been made when this special issue went to press in the spring of 1997:

- *National Institutes of Health independent consensus panel:* No single recommendation for screening of all women in this age group. After weighing the benefits and risks with her doctor, each woman should decide whether to have yearly mammograms before age 50.
- *National Cancer Institute:* Mammography screening every one to two years.
- *American Cancer Society:* Mammography screening once a year.

The differences in recommendations stem from differences in interpretations of the studies. According to the NIH panel experts, studies do not show that yearly mammographic screening has clear benefits for women in their 40s when relative risks for women in this age group are taken into account. These risks include a higher percentage of false-positive readings than for older women (30 percent of women aged 40 to 49 who have mammograms are told an abnormality exists when none does). These false-positive readings can result in unnecessary tests and surgery. When women in this age group undergo biopsies after a positive mammogram, half as many cancers are found as among women aged 50 to 59. Of every eight biopsies in the 40-to-49-year-old age group, one invasive and one *in situ* breast cancer is found. In addition, the rate of false-negative readings is high in this group: In women 40 to 49 years old, mammography misses 25 percent of invasive breast cancer compared with 10 percent in older women.

Further, the NIH panel said that studies showed no differences in breast cancer death rates within seven years between women in their 40s who had had mammography and those who had not.

Nevertheless, there may be compelling reasons for yearly mammograms for women in their 40s. For example, although the studies individually did not show a clear-cut benefit, when data from all the studies were pooled, they showed about a 17 percent reduction in deaths among women who had had mammograms. In addition, most of the studies included only white women. Although the incidence of breast cancer is about the same for white and African American women, in this age group, African American women have a 50 percent higher breast cancer death rate than white women.

It is important to note that all age-related screening recommendations apply to women who have no symptoms of breast cancer and who are not at increased risk for the disease. Any woman, regardless of age, should see her doctor immediately if she has symptoms, such as a lump, nipple discharge, or other change in the breast. And, for women who have no symptoms but may be at higher risk because of genetic or family history, or late childbearing, for example, a physician may recommend earlier and more frequent mammograms.

It is important that mammography be of the highest possible quality. Mammography can fail to do its job due to poor technique in taking, processing or reading the films; inadequate record keeping and reporting of results; and lack of effective quality controls.

The concern that facilities varied in the quality of mammograms performed and the desire for high-quality mammography in all facilities resulted in Congress passing the Mammography Quality Standards Act (MQSA) in 1992.

FDA has the responsibility for implementing and enforcing the MQSA. In December 1993, the agency set forth standards that mammography professionals and facilities would have to meet by Oct. 1, 1994, or stop doing mammography. When this special issue went to press, FDA was expected to publish final rules later in 1997.

In accordance with the law, all mammography facilities must be certified by FDA-approved accreditation bodies. To be certified, a facility must meet quality standards for x-ray images, equipment and personnel and must be inspected annually. By early 1997, all U.S. facilities had been inspected at least once, and two-thirds had had their second annual inspection. There are now about 10,060 certified mammography facilities in the United States.

When selecting a facility, women should find out if it is certified by FDA. If a facility is certified by FDA, Medicare will provide reimbursement for qualified patients. Women who have breast implants should ask if the facility uses special techniques designed for women with implants.

FDA has posted a list of facilities it has certified, divided by state, at *http://www.fda.gov/cdrh/faclist.html* on the agency's World Wide Web site. ■

said P. Andrew Futreal, M.D., one of the Duke University researchers. "Our findings strongly suggest that BRCA2 accounts for the remaining 50 percent."

Scientists have estimated that BRCA1 and BRCA2 mutations occur in more than 2 out of 100 Ashkenazi Jews. A study reported in the May 15, 1997, issue of the *New England Journal of Medicine* by Michael Krainer, M.D., and colleagues concludes that BRCA2 mutations may contribute to fewer cases of breast cancer in younger women (early onset) than do BRCA1 mutations. BRCA2 alteration appears to increase a woman's lifetime risk of ovarian cancer to about 10 percent. Families with the BRCA2 alteration also appear to have higher rates of male breast cancer, prostate cancer, and ocular melanoma (a type of eye cancer). A specific BRCA2 alteration, called 6174delT, has been identified in Ashkenazi Jewish families.

Most scientists in this field recommend that testing for these genes be limited to research in which subjects are members of families at high risk for either ovarian or breast cancer, and that genetic counseling and risk assessment—including the possibility of false-negative and false-positive results—be provided. A two-part report in the March 19 and March 26, 1997, issues of the *Journal of the American Medical Association* presents guidelines for doctors from the Cancer Genetics Studies Consortium, composed of government and nongovernment experts and organized by the National Human Genome Research Institute. The guidelines advise doctors to counsel patients to consider all ramifications of genetic tests before being tested. The guidelines also say that women who carry either of the BRCA genes should begin monthly breast self-exams when they are 18 to 21 years old and annual mammograms and breast exams by a health professional between the ages of 25 and 35.

Some women with a high genetic risk of breast cancer consider breast removal (when no cancer is present) as a way to prevent cancer. Such prophylactic surgery is controversial. A study reported by Deborah Schrag, M.D., and colleagues in the May 15, 1997 issue of the *New England Journal of Medicine* estimates that, on the average, 30-year-old women who carry BRCA1 or BRCA2 mutations gain about 3 to 5 years of life from such surgery. Gains in life expectancy decline with age and by the time a woman is 60 disappear. Women considering prophylactic surgery should be aware of all the issues involved, including the fact that such surgery does not completely eliminate the possibility of cancer.

Women considering prophylactic surgery should be aware of all the issues involved, including the fact that such surgery does not completely eliminate the possibility of cancer.

Other Genetic and Risk Factors

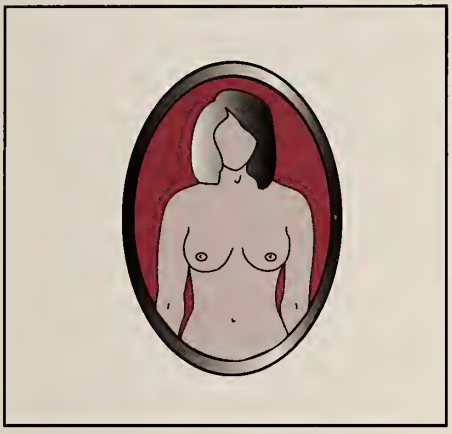
The first tumor suppressor gene associated with breast cancer was reported in the Nov. 30, 1990, issue of *Science* by Stephen H. Friend, M.D., Ph.D., of the Massachusetts General Hospital Cancer Center. Certain alterations in a tumor suppressor gene called p53 lead to a rare syndrome involving increased susceptibility to a number of cancers, including early-onset breast cancer, certain childhood cancers, brain tumors, leukemias, and a tendency to develop multiple tumors. About 100 families around the world have been identified with this rare syndrome, named Li-Fraumeni for the two scientists who first described it in 1969. Follow-up of the four families originally identified 16 new cancer cases when only one would have been expected. Other relatively rare genetic mutations are also known to be associated with an increased risk of breast cancer. Certain types of benign (noncancerous) breast disease and radiation exposure are also established risk factors. Among postmenopausal women, obesity is associated with an increase in risk.

A link between radiation and breast cancer was established from studies of survivors of Hiroshima and Nagasaki and of women who had undergone radiation therapy or had repeated fluoroscopy, which was used many years ago to treat tuberculosis. The interval between exposure and disease development varies, but, according to Bates, the average is 20 years.

Women who begin menstruating before age 12, become menopausal after 50, delay childbearing until after 30, or who bear no children are also at higher risk. On the other hand, the risk is lower

Breast Self-Examination (BSE)

Breast self-examination should be done once a month so you become familiar with the usual appearance and feel of your breasts. Familiarity makes it easier to notice any changes in the breast from one month to another. Early discovery of a change from what is "normal" is the main idea behind BSE. If you menstruate, the best time to do BSE is two or three days after your period ends, when your breasts are least likely to be tender or swollen. If you no longer menstruate, pick a day, such as the first day of the month, to remind yourself it is time to do BSE.



1. Stand before a mirror. Inspect both breasts for anything unusual, such as any discharge from the nipples, puckering, dimpling, or scaling of the skin.

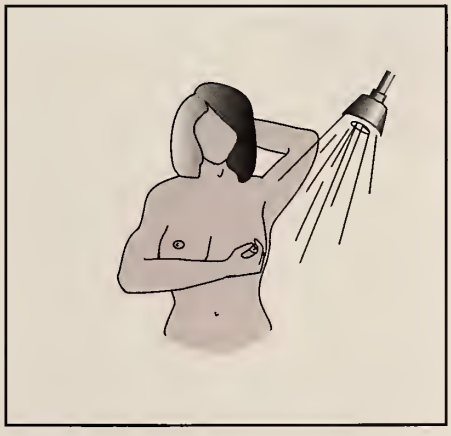
The next two steps are designed to emphasize any change in the shape or contour of your breasts. As you do them, you should be able to feel your chest muscles tighten.

2. Watching closely in the mirror, clasp hands behind your head and press hands forward.

3. Next, press hands firmly on hips and bow slightly toward the mirror as you pull your shoulders and elbows forward.

Some women do the next part of the exam in the shower. Fingers glide over soapy skin, making it easy to concentrate on the texture underneath.

4. Raise your left arm. Use three or four fingers of your right hand to explore your left breast firmly, carefully and thoroughly. Beginning at the outer edge, press the flat part of your fingers in small circles, moving the circles slowly around the breast. Gradually work toward the nipple. Be sure to cover the entire breast. Pay special attention to the area between the breast and the armpit, including the armpit itself. Feel for any unusual lump or mass under the skin.



5. Gently squeeze the nipple and look for a discharge. Repeat the exam on your right breast. (If you have any discharge during the month—whether or not it is during BSE—see your doctor.)

6. Steps 4 and 5 should be repeated lying down. Lie flat on your back, left arm over your head and a pillow or folded towel under your left shoulder. This position flattens the breast and makes it easier to examine. Use the same circular motion described earlier. Repeat on your right breast. ■

in women who have their first child before age 18 and in women who, because of surgical removal of the ovaries, become menopausal before age 35.

However, the American Cancer Society points out that about 25 percent of breast cancer cases occur among women with no major risk factors, so all women should consider themselves at risk.

Possible Risks

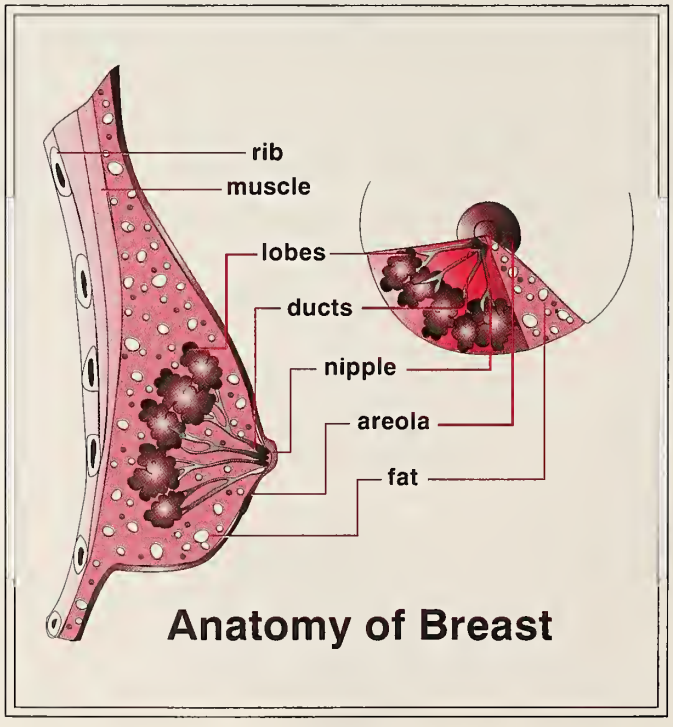
Reserpine (a drug for high blood pressure marketed as Rogroton, Ser-Ap-Es, Hydropres, and others), hair dye chemicals, cigarette smoking, alcohol consumption, dietary fat, birth control pills, and estrogen therapy have all been suggested as risk factors, but results from various studies have been contradictory, and their role in disease development remains controversial.

Some research has indicated that birth control pills might increase the risk of breast cancer, particularly in premenopausal women between the ages of 45 and 55, in women with a family history of breast cancer, or among young women who use them before the first pregnancy. One long-term study, however, reported that neither short-term nor long-term (more than 11 years) use appeared to increase risk, even in these groups of women. For now, the Food and Drug Administration requires that birth control pills carry a label indicating that the association between oral contraceptives and breast cancer is not clear.

Women who receive estrogen replacement therapy (ERT) may also be at increased risk. ERT is recommended for some menopausal women to counteract hot flashes and sweating and to slow bone thinning (osteoporosis). ERT may also confer protection from cardiovascular disease. A study of 118,000 female nurses followed for 10 years found a "modest" increase in breast cancer risk in current users—more so with increasing age—but not in past users, even if therapy had lasted more than 10 years. The researchers, led by Graham Colditz, M.B., B.S. (British equivalent of M.D.), of Brigham and Women's Hospital in Boston, concluded that, "Though this increase in risk will be counterbalanced by the cardiovascular benefits, [there is a] need for caution in the use of estrogens."

It is not clear whether the addition of progestin to this regimen has any effect on breast cancer risk.

Another hormone scientists are investigating in relation to breast cancer is DES (diethylstilbestrol), prescribed a generation ago to prevent miscarriage and to prevent lactation after childbirth, and linked with vaginal cancer in daughters of mothers who took it while pregnant.



The possible relation of a high-fat diet and alcohol intake to breast cancer is also being investigated. The death rate from breast cancer is highest in countries, including the United States, in which the intake of fat and animal protein is high. For instance, Japanese women historically have a low risk for breast cancer, but that risk has been rising dramatically, concurrent with a "Westernization" of eating habits—that is, from a low-fat to a high-fat diet. Within Japan, the risk is 8.5 times higher for wealthier women, who eat meat daily, than among poorer women.

When large populations move from a low-incidence area to a high-incidence area and adopt the local lifestyle, they tend to take on the cancer risk patterns of their new homeland. Among immigrants from Asia to the United States, the incidence of breast cancer typically rises somewhat in the first generation, then continues to rise in subsequent generations until it approaches that of women born in the United States.

A study involving nearly 57,000 women published in the March 6, 1991, *Journal of the National Cancer Institute,* found an association between breast cancer and fat intake that, the authors say, "appears unlikely to have arisen by chance," even though the link is not strong and two previous studies contradict their results. It could be that the issue is unclear because the difference in fat content between the lower fat and higher fat diets of the women studied may not be great enough to influence breast cancer development. Americans typically consume 40 percent of their calories in fat. A reduction to 30 percent may not be significant in reducing breast

cancer risk.

To examine the question further, NIH's Women's Health Initiative includes a study of women aged 50 to 69 comparing those who greatly reduce their fat intake with those who don't to see how this difference in diet affects the incidence of breast cancer, colorectal cancer, heart disease, and overall mortality.

These risk factors may appear unrelated, but a possible common thread may be estrogen. Estrogen causes breast cells to grow, and there may be times in a woman's life when the breast is more susceptible to cancer-causing substances in the environment. A longer menstrual history, the additional estrogens from birth control pills or from ERT, or even a high-fat diet, alcohol intake, or just being overweight may increase the amount of estrogen in the bloodstream, increasing the amount available to the woman's breast tissue.

Anatomy of a Disease

The breast is a gland designed to produce milk. Milk ducts leading to the nipple originate from lobules inside 15 or 20 lobes arranged like spokes around a wheel. The spaces around and between the milk-producing lobes are filled with fat. About 90 percent of breast cancers arise from the milk ducts. When ductal carcinoma, as it is called, remains confined to the duct, it is called *in situ,* or intraductal, cancer. When the cells penetrate the walls of the duct and invade surrounding tissue, it is called invasive ductal cancer. About 5 percent of breast cancers are lobular carcinomas, which originate in the lobules.

Two atypical kinds of breast cancers are inflammatory breast carcinoma and Paget's disease. While most breast cancers are slow growing and painless, inflammatory breast cancer progresses very rapidly and is painful, with symptoms resembling an infection. The breast is warm and reddened, and the skin may appear pitted like an orange peel. In Paget's disease, the nipple becomes crusted; cancer cells grow upward along the ducts from a malignancy (cancer) deeper in the breast.

When an abnormality is detected in the breast by mammography (see "Mammography: A Lifesaving Step"), the doctor may recommend a biopsy. If a lump is found by palpation (feeling the mass), a biopsy is almost always necessary. Exceptions may be certain lumps found in women who have histories of lumpy or cystic breasts, and in some fluid-filled and solid tumors when imaging methods in addition to mammography are used. Any woman noticing a lump—especially if newly developed—should consult her doctor.

To help differentiate benign from cancerous tumors, in April 1996, FDA approved an additional use for a high definition ultrasound system as an adjunct to mammography and physician breast exam. The Ultramark 9 High Definition Imaging (HDI) Ultrasound System Level 3, originally cleared for marketing in 1991 for general-purpose imaging, including whether breast tumors are fluid-filled or solid, can now also be used to help assess whether a solid tumor is likely to be benign (fluid-filled tumors in younger women are almost always benign). Before this approval, solid tumors had to be biopsied to ensure correct diagnosis. The HDI system is approved for use in diagnosing tumors that are at least 1 centimeter (about three-eighths of an inch) in diameter.

The biopsy usually involves surgical removal of all or part of the lump or suspicious area, allowing a pathologist to examine the tissue and determine with certainty whether or not the lesion is cancerous. Some biopsies are done by fine needle aspiration, using a local anesthetic. The doctor inserts a needle into the lump and tries to withdraw fluid. If it is a cyst, it will collapse when the fluid is removed. If it is solid, the doctor may remove some cells with the needle to send to the laboratory for analysis. About 80 percent of palpable lumps are benign (not cancerous).

Biopsy does not always require hospitalization. It can be done as an outpatient procedure. Until the late 1970s, it was standard procedure for the patient having a biopsy to sign a consent form permitting the surgeon to remove the breast at the same time if the tumor was found to be cancerous. The common practice nowadays is to do a biopsy first and then schedule surgery, if necessary, within the next few weeks. Some women may still choose the one-step procedure that was routine when Joyce Fine had her mastectomy.

The interval with the two-step procedure, however, allows the woman time to find out about and choose among her treatment options, get a second opinion, and prepare for her hospital stay. The brief delay in treatment does not reduce the chances for a successful outcome. Some states have passed laws requiring that women be told a two-step procedure is their legal right and, in some cases, that they be given specific information about their options.

Progress in Therapy

The treatment options women have today were not available to Joyce Fine when she had her mastectomy—a Halsted radical. This entailed removing the entire breast, underlying chest muscles, all the axillary (underarm) lymph nodes, and some additional fat and muscle. Fine's surgeon did not discuss with her possible treatment alternatives. The Halsted radical was the standard treatment for breast cancer in 1972.

"There was no discussion," Fine recalls. "He convinced me I had to have the tumor out as soon as possible and that I should sign a release that if they find at biopsy that it's cancerous, they should remove it right away."

The surgeon acknowledged that Fine

could have a two-step procedure. "But he said that if I go that way, it would metastasize [spread] and I couldn't be put under anesthesia again soon," she says. "It would be a waiting period of a couple of weeks, and I was so frightened I said I'd do it in one procedure. He made me feel as though if I didn't, I might be dead in two weeks."

And so, like so many women with breast cancer then, Fine went into surgery not knowing if she would leave the hospital physically the same as she entered, or minus one breast as the result of extensive, disfiguring surgery.

"Beginning in the 1940s, studies were suggesting that so much surgery was not necessary," said NCI's Bates. "In Europe, by 1971, smaller operations were accepted, but in the United States, change was slow in coming. Surgeons were reluctant to abandon the Halsted radical mastectomy for fear of giving inadequate treatment."

Treating Early-Stage Disease

Both the Halstad surgery and the process Fine experienced now belong to medical history. It is generally agreed that radical surgery is not helpful if the cancer has spread, and not necessary if the cancer has not spread. Surgical treatment now emphasizes breast conservation—preserving the breast when possible. Lumpectomy (also called segmental mastectomy or tylectomy), in which only the tumor and a margin of surrounding tissue is removed, is now common treatment for breast cancer. This procedure is light years away from the Halsted radical, both in its physical and psychological effects.

Radical mastectomy was based on the rationale that breast cancer started with a tumor in the breast and, over time, spread in an orderly fashion to the lymph glands under the arms and then, through the lymph and blood, to other parts of the body—usually the lungs, liver, bone, or brain. Halsted's procedure was designed to remove the avenues of possible spread.

By the late 1970s, experts had determined that the Halsted radical mastectomy was not necessary. This conclusion was based on research that changed the

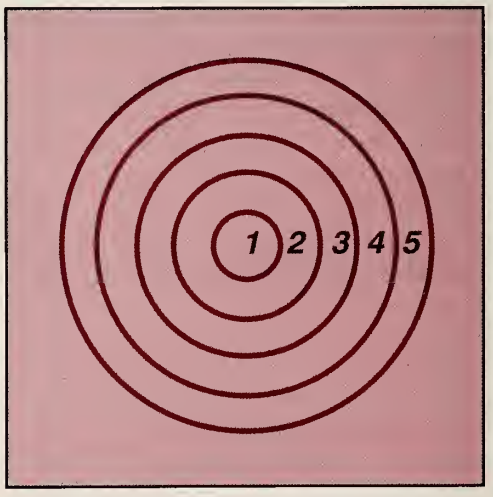
Determining Therapy

Treatment is based on the extent of the disease and the biology of the specific tumor. Evaluation of these factors guides the approach of surgery and, if needed, adjuvant therapy. In addition, a woman's age and menopausal status are significant. Breast cancer tends to be more aggressive in younger, premenopausal women.

First, based on tumor size and degree of cancer spread, the disease is classified into one of the following stages:

- **Carcinoma *in situ*:** Very early breast cancer that has not invaded nearby tissues.
- **Stage I:** Localized tumor no larger than 2 centimeters (cm) (about 1 inch).
- **Stage II:** Tumor no larger than 2 cm, but the cancer has spread to the underarm lymph nodes, *or* tumor between 2 and 5 cm (about 2 inches) and cancer may not have spread to the lymph nodes, *or* tumor bigger than 5 cm, but cancer has not spread to the lymph nodes.
- **Stage III:** Tumor larger than 5 cm and cancer has spread to underarm lymph nodes, *or* tumor smaller than 5 cm and the underarm lymph nodes have grown into each other or into other tissues, *or* the tumor has spread to tissues near the breast (such as the chest muscles and ribs) or to lymph nodes near the collarbone, *or* it is inflammatory breast cancer.
- **Stage IV:** The cancer has spread to other organs of the body, usually the lungs, liver, bone, or brain.

Carcinoma *in situ* has a cure rate approaching 100 percent with surgery alone. Tumors of 1 cm or less also carry a particularly good prognosis—less than 10 percent recurrence in 10 years. In general, the risk of recurrence rises with increasing tumor size and lymph node involvement.



Tumor sizes in centimeters.

Breast tumor tissue can be examined for important "markers" that give clues to the aggressiveness of the disease and can, therefore, help guide therapy. Some of these markers are:

- **Estrogen and progesterone receptors.** Patients whose cancer cells have proteins (receptors) to which these hormones bind have a better prognosis because the cells can be treated with hormone therapy.
- **Histologic type.** Breast cancers vary in their cell type. For example, invasive ductal cancers can sometimes be categorized into further subtypes, such a mucinous, tubular and medullary. Lobular cancers are another cell type. The various types have different rates of growth and spread.
- **DNA studies.** The degree of disruption of DNA in the cell nucleus correlates with the disease aggressiveness. The more disarrayed the DNA, the greater the risk of relapse. Also, cells that divide more rapidly carry a poorer prognosis.
- **HER-2 oncogene.** This gene is sometimes found in tumors of patients whose cancer has spread. Detected early, it might predict spread and identify patients who would benefit from more aggressive treatment.
- **Cathepsin D.** High levels of this protein are associated with a poorer prognosis. Secreted by the cancer cells, cathepsin D may aid their spread to other parts of the body. ■

—M.S.

Reconstruction Options

Breast reconstruction after mastectomy used to be very complex, and the results were often disappointing. So, as recently as a generation ago, few women chose to have it done and many were not aware it was a possibility. In the last quarter of this century, however, advances in plastic surgery have made breast reconstruction easier, more successful, and more popular.

Still, not every woman who has had a mastectomy chooses reconstruction. Some women decide against it because they don't want to have more surgery or they feel the risks outweigh the benefits or for other reasons. Many women prefer to wear breast forms (prostheses).

For women who desire reconstruction, however, there are few limitations. Even women who have had radical surgery or whose skin has been grafted, damaged by radiation therapy, or is otherwise thin or tight can have successful reconstructive surgery.

Although some women have breast reconstruction during the same surgery as their mastectomy, many surgeons recommend waiting three to six months. This allows time to complete radiation or chemotherapy and for the mastectomy incision to heal.

Three major types of breast reconstruction are available.

Implant Placement

There are two types of breast implants currently available for reconstruction patients. One is filled with saline (salt water), the other with silicone gel. Both types have a silicone envelope. Since April 1992, the use of silicone gel-filled implants has been limited to women participating in clinical trials designed to evaluate the risks and benefits of the devices. Saline implants are available without restriction. (See "A Status Report on Breast Implant Safety," page 100.)

The most common problem associated with both saline and gel-filled breast implants is capsular contracture. This occurs when scar tissue shrinks around the implant, making it feel hard and sometimes misshaping it. Other known health risks include incorrect mammography results, implant rupture, and change in breast sensation, which may be temporary or permanent.

In addition, silicone gel can escape from gel-filled implants because of rupture. Small quantities of silicone also "bleed" from intact implants.

Like the silicone gel-filled devices, saline implants have a silicone rubber envelope and may not be entirely without risk. In addition, with leakage or rupture, saline implants deflate and usually must be replaced. Women considering implants need to be aware that repeat surgeries may be required.

Latissimus Dorsi

"Latissimus dorsi" reconstruction gets its name from the broad flat back muscle that the surgeon moves to the chest to take the place of muscles that have been removed during the mastectomy. The surgeon also transfers skin and other tissue from the patient's back to the mastectomy site. An implant is then placed under the new muscle, and drains may be inserted temporarily. This operation takes longer and requires longer hospitalization than simple implant placement. It leaves a scar on the back in addition to the mastectomy scar on the chest.

Rectus Abdominus

In this procedure, the surgeon transfers one of two abdominal muscles to the breast area, along with skin and fat from the abdomen. The surgeon shapes this flap of muscle, skin and fat into the contour of a breast. If there is enough abdominal tissue available, no implant is needed. This procedure leaves a horizontal scar across the lower abdomen in addition to the mastectomy scar.

Nipple and Areola Construction

Breast reconstruction fashions the shape of the breast but does not always include a reconstructed nipple and areola (the dark skin around the nipple). Some women, who wish primarily to improve their appearance in clothing, choose not to have the additional one- to two-hour operation to reconstruct the nipple and areola. During this operation, the areola is usually fabricated from skin on the upper thigh or from behind the ear, and the nipple is created either from tissue from the newly created breast mound or from the other nipple. If the reconstructed areola is not dark enough, ultraviolet light can be used to darken the skin.

Although breast reconstruction offers a more normal appearance both in and out of clothes, women should be aware that if there are scars from these operations they are permanent and that reconstruction does not restore lost sensation. ■

concept of how breast cancer progresses. It is now understood that very early in the disease (although exactly how early is not known), breast cancer cells travel through the blood and lymph to other parts of the body. In this process, called micrometastasis, the cancer is so small it can't even be detected with a microscope. In other cases, depending on the biology of the cancer cells, the cancer may remain in the breast without spreading until later in the course of the disease.

Treatment now emphasizes removing the tumor while sparing the breast. By examining tissue taken during surgery, doctors can see if tumors may have spread. Patients with such tumors then can receive additional therapy, which may include radiation, chemotherapy (drugs that kill cancer cells), hormone therapy, or a combination.

As new approaches to surgical and medical treatment have been tried, each method has had its supporters and dissenters. In 1957, NCI organized the National Surgical Adjuvant Breast Project to create a pool of data gathered from research on breast cancer treatments. In the late 1970s, scientists reviewed study results and determined that simple, or total, mastectomy, in which only the breast was removed, was as effective as the Halsted radical.

Then, in 1990, at an NIH consensus development conference on treatment of early-stage breast cancer, a panel of experts agreed that still less-extensive surgery, lumpectomy, gave the same results if radiation followed surgery to kill any remaining cancer cells. The lymph nodes are also removed for examination during this procedure.

The panel concluded that breast conservation treatment is not only appropriate for most women with early-stage disease but also "is preferable because it provides survival equivalent to total mastectomy and also preserves the breast. Total mastectomy remains an appropriate primary therapy when breast conservation is not indicated or selected."

Women who have multicentric breast cancer (cancers that develop at several locations within a single breast), or whose tumors are large relative to breast size and therefore would not have a good cosmetic result, are among those who may not be candidates for breast conservation.

No single procedure can be recommended as ideal for all patients. Women and their surgeons must base their decisions on the patient's medical status and her particular concerns. Her choice may be influenced by emotional considerations, finances, access to care, body image, and personal beliefs.

Following either mastectomy or lumpectomy with radiation, additional (adjuvant) therapy is given to most women whose cancer has spread to the lymph nodes. This may be chemotherapy or hormone therapy, or both. A current controversy in treatment concerns whether or not to treat node-negative breast cancer patients (patients in whom the disease has not spread to the lymph nodes) with adjuvant therapy, since these additional treatments to improve the outcome can also have side effects. Seven of 10 node-negative women will never have a recurrence of disease. Of the remaining three, standard adjuvant therapy will prevent recurrence in one.

Unfortunately, there is no way yet to predict which three will have a recurrence, nor which one of those will be helped by adjuvant treatment. The dilemma, says Bates, is, "Do we treat 10 to help one, and potentially three, if our treatments can improve?"

Many drugs have been tried alone and in combination to find the best treatment. Cancer drugs can have serious side effects. They are designed to kill cancer cells, but they also affect other rapidly growing cells, such as blood-forming cells in the bone marrow and those that line the digestive tract. As a result, they may lower resistance to infection, sap energy, and cause bruising or bleeding, nausea, vomiting, mouth sores, loss of appetite, hair loss, reduced heart function, and other side effects. Premenopausal women may also experience hot flashes, vaginal dryness, painful intercourse, and irregular menstrual periods.

Side effects of chemotherapy vary with each patient, according to the treatment given and the individual's reaction. Severe vomiting can be a problem. However, FDA has approved drugs such as Zofran (ondansetron hydrochloride) to treat the nausea and vomiting associated with chemotherapy. Marinol (oral marijuana derivative) has also been effective in selected cases.

Tamoxifen

An oral drug called tamoxifen (marketed as Nolvadex) is most often given to women whose cancer cells are estrogen-receptor positive—that is, their growth is likely to be encouraged by estrogen. Tamoxifen interferes with the activity of estrogen, thus keeping the cells from getting the hormones they need to grow. Originally approved by FDA in 1977 for patients with advanced breast cancer and subsequently for patients with less severe disease, tamoxifen was also approved for use in node-negative patients in June 1990.

Tamoxifen slows or stops the growth of cancer cells already present in the body and helps prevent recurrence and development of cancer in the other breast. Though the drug counters the effects of estrogen in breast tissue, it acts like estrogen in other parts of the body, so that women taking the drug may receive benefits similar to that of hormone replacement therapy, such as lowering of blood cholesterol and slowing of bone loss after menopause.

Possible adverse effects include a risk of blood clots similar to birth control pills, and an elevated risk of uterine cancer. More common but less serious side effects include hot flashes, nausea and vomiting. Patients may also experience visual changes and develop cataracts.

FDA has approved a blood test to help

determine whether breast cancer has recurred. Called the Truquant BR Radioimmunoassy Kit, it measures an antigen found in the blood of patients with breast cancer, as well as other types of cancer. Test results can be analyzed within a few hours in a hospital lab. However, because there can be false-positive and false-negative results, it is not intended as the sole basis for detection of cancer recurrence. This diagnosis can only be made after the test results are verified by other diagnostic procedures.

Treating Advanced Disease

Breast cancer that has advanced to Stage III or IV (see accompanying article, "Determining Therapy") requires chemotherapy or hormone therapy, or both, to treat its spread. Treatment may also include surgery or radiation therapy, or both, to control the breast tumor. Hormone therapy may be accomplished with drugs such as tamoxifen or, in premenopausal women, by removing the hormone-producing ovaries. Women whose cancer has spread beyond the breast to other parts of the body usually have less extensive breast surgery, but receive hormonal therapy or more aggressive chemotherapy directed to treating both local and metastatic disease. If necessary, radiation may be used for local control.

Most tumors eventually become resistant to anticancer drugs and continue to grow. New treatments under study for patients with advanced breast cancer involve removing some of the patient's bone marrow and administering chemotherapy at very high doses to overcome drug resistance. This is followed by reinfusing the bone marrow to prevent life-threatening drug toxicity. This therapy is also being tried in patients at high risk of disease recurrence.

Other means of reversing drug resistance with various agents are under study. One such agent, verapamil (approved for treating high blood pressure), has been shown in laboratory studies to block a cell surface protein that pumps chemotherapy drugs out of a cell, thereby making it drug resistant.

Fortunately, most breast cancers are now detected at the earlier, more treatable stages. According to NCI, about 59 percent of women diagnosed with breast cancer in 1986-1992 had small, localized tumors, and about 32 percent had cancer that was regionally confined. According to the American Cancer Society, the five-year survival rate for localized breast cancer has risen from 78 percent in the 1940s to about 96 percent today. However, some breast cancers, even though localized, will recur after five years. The overall 10-year survival rate is 65 percent, and after 15 years it is 56 percent.

Though much progress has been made, much remains to be done. For example, though death rates have begun to fall for the general population, in certain groups, such as African Americans, they are not decreasing as rapidly as in the general population. This points out the need for continued education about diagnosis and treatment. Too, knowledge about the role of heredity and the environment in this disease is still unfolding.

And research continues. Some areas of investigation include alternate methods of diagnosis, such as 3-dimensional x-rays and other forms of imaging, simpler biopsy procedures, and more effective drugs and combinations of drugs.

It is important to remember that every woman should consider herself at risk for breast cancer. A woman's best tool in fighting this disease is knowledge—of her body (through examination by a health professional, mammography, and breast self-exam), of her family history, and of other risk factors. Such knowledge can go far to ensure early diagnosis and prompt treatment if she should be among the 12 percent of American women stricken with breast cancer during their lives. ■

Marian Segal is a member of FDA's public affairs staff. Judith Levine Willis is editor of this special issue.

For More Information

Here are the phone numbers and World Wide Web addresses of some of the many sources of breast cancer information:

General Information

National Cancer Institute's Cancer Information Service (CIS)
(1-800) 4-CANCER (1-800-422-6237)
http://icicsun.nci.nih.gov/occdocs/cis/cis.html

NCI's CancerNet
http://wwwicic.nci.nih.gov/

National Alliance of Breast Cancer Organizations (NABCO)
(1-800) 719-9154
http://www.nabco.org/

The American Cancer Society
(1-800) ACS-2345 (1-800-227-2345)
http://www.cancer.org/bcn.html

Y-ME National Breast Cancer Organization
(1-800) 221-2141
http://www.y-me.org/index.html

OncoLink
http://www.oncolink.upenn.edu/disease/breast/

Breast Cancer Information Center
http://feminist.org/other/bc/bchome.html

EduCare, Inc.
http://www.cancerhelp.com/ed/

Mammography

List of FDA-certified mammography facilities
http://www.fda.gov/cdrh/faclist.html

American College of Radiology
http://www.acr.org/

Heart Disease

Number One Killer Of Women

by Margie Patlak

In the spring of her 58th year, Anita Chudnow of Milwaukee, Wis., was working in her garden when a sudden and extreme fatigue overcame her. She went in to lie down and didn't have the energy to get up to make dinner several hours later.

Convinced that something was amiss, her family insisted she see a doctor. He put her through a battery of tests, which revealed that three of Chudnow's heart arteries, called coronaries, were choked with a fat-like deposit called plaque. The plaque had narrowed her arteries, depriving her heart of the oxygen-rich blood it needed to function.

"I couldn't believe it," said Chudnow, recalling her surprise at learning she had coronary heart disease, although she was familiar with the condition because her father had it. "Maybe I thought heart disease was a man's disease because of all those years my father suffered from it. I went with him in the ambulance to the hospital so many times and I never thought the same thing could happen to me," she said.

Unfortunately, Chudnow isn't the only one with that misconception. Although heart disease has been the number one killer of women since shortly after the turn of the century when it overtook infectious diseases, most people aren't aware of how common—and how deadly—the disorder is in women.

"This is a problem," said cardiologist Nanette Wenger, M.D., of Emory University in Atlanta, "because unless women see heart disease as part of their disease profile, they're not going to adhere to heart disease prevention messages early in life and they're not going to respond to heart disease symptoms later on."

The lack of awareness of heart disease in women was fueled, in part, by the early findings of the landmark Framingham Heart Study. In this study, which began in 1948 and is still ongoing, researchers have scrutinized the habits and health of thousands of middle-aged men and women from Framingham, Mass. After collecting data for a little over a decade, they found that three times more men died from heart disease during this period than women, which led to the conclusion that women were somewhat protected from the condition.

Further analyses of the Framingham data and a study conducted at the Cleveland Clinic revealed, however, that women aren't spared from medical matters of the heart, but rather tend to develop them about 10 to 15 years later in life than men. According to the American Heart Association, 1 in 9 women aged 45 to 64 has some form of heart or blood vessel disease; this ratio soars to 1 in 3 at age 65 and beyond. The approximately 500,000 heart attack deaths that occur annually in this country, in addition, are evenly split between men and women. Each year, nearly twice as many women die from heart disease and stroke as from all forms of cancer combined.

Despite the prevalence and seriousness of heart disease among women, much of what is known and popularized about it is based on research done in men. The studies that have included women suggest, however, that many of

ILLUSTRATION BY JACK PARDUE

Most people aren't aware of how common—and how deadly—heart disease is in women.

the mainstays of diagnosis, treatment and prevention of coronary heart disease may not apply to the female gender.

As with other drugs and populations, the Food and Drug Administration is responsible for the safety and effectiveness in women of medications for heart disease.

Discrepancies in Diagnosis

One of the telltale signs of heart disease is chest pain or tightness, known as angina, that occurs during physically demanding tasks such as climbing stairs, or under emotional strain. This pain can make a person short of breath. It can radiate to the jaw, neck, shoulders, or inner arms. Angina occurs because narrowed arteries in the heart deprive it of oxygen-rich blood. If a blood clot completely chokes off the blood supply in these arteries in what is known as a heart attack, chest pain usually becomes more severe and lasts longer.

But chest pain may not be as good a diagnostic clue of serious heart disease in women as it is in men. Nearly twice as many men as women with chest pain that may be angina actually have coronary heart disease. This finding is from the National Institute of Health's Coronary Artery Surgery Study. It may stem, in part, from women being more likely than men to have such conditions as heartburn or spasms of the esophagus or heart arteries, which can cause chest pain that resembles angina.

But given the dire consequences of heart disease that goes unrecognized, Wenger said that any woman complaining of chest pain should be taken seriously by her doctor. She and other experts at a 1992 conference convened by the National Heart, Lung, and Blood Institute recommended that doctors carefully evaluate women (and men) with chest pain, based on their symptoms and risk factors for heart disease, such as smoking or high blood pressure. These patients should then have tests to detect abnormalities prompted by narrowed heart arteries or a previously unrecognized heart attack.

But some of these commonly performed tests are less accurate in women then men and have prompted some cardiologists to reject their use in female patients altogether. One standard test is an exercise stress test, during which the patient exercises on a treadmill while the activity of the heart is electrically monitored. But this test falsely predicts heart disease in as many as half the women tested, studies show. In addition, many women cannot exercise long enough for such a test because, at their older age, they have exercise-limiting illnesses, such as arthritis.

To improve this situation, researchers have developed statistical standards for the treadmill stress test in women that use a woman's age and risk factors for heart disease to improve accuracy. Wenger is satisfied enough with these modifications to prescribe the treadmill stress test for her female patients, if they can exercise. But other cardiologists still question its accuracy because they think most doctors don't have the information they need to adequately assess a woman's risk factors for heart disease. "I don't do stress treadmill tests in women," said Marianne Legato, M.D., of Columbia University.

Legato prefers women to exercise while the heart's activity is monitored by ultrasound in what is known as a stress echocardiogram. Experts agree that this test is accurate in both men and women, as is the thallium exercise stress test, in which blood flow to the heart is imaged during exercise with radioactive tracers injected into a vein. Adjustments must be made for a woman's breast tissue, however, which can obscure the radioactive signals emitted from heart arteries.

None of these tests can effectively and practically screen on a routine basis symptom-free men or women for heart disease. This is unfortunate because women are more likely than men to have "silent" or unrecognized heart attacks.

Part of the reason more women have undetected heart attacks, according to Legato, is because women often have signs of a heart attack that differ from those typical in men. Women are more likely than men to have nausea and pain high up in the abdomen or burning in their chest during a heart attack. "Women ought to be careful of what they're calling 'indigestion'," Legato said.

Other women, such as Chudnow, have atypical angina that includes extreme fatigue on physical exertion rather than chest pain.

Deadly Difference

Whether silent or replete with telltale symptoms, heart attacks or their aftermath tend to be more deadly in women. About one-quarter more women than men die within a year of having a heart attack. This difference may stem from women generally being older than men when they suffer heart attacks. (Their older age makes them more likely to have other illnesses that hamper survival.) Also, women do not respond as well as men to treatments for heart disease usually prescribed during or after a heart attack.

These treatments include coronary angioplasty. In this procedure, a tiny balloon is inserted into blocked heart arteries and their branches, and then inflated to compress the plaque that is obstructing the flow of blood to the heart. A study by Sheryl Kelsey, Ph.D., of the University of Pittsburgh found that women were 10 times as likely as men not to survive coronary angioplasty. When women and men of the same age and with the same history of heart disease were compared, women's risk of death during the procedure was still nearly five times higher than men's.

Other studies show that women are twice as likely as men to have heart disease symptoms four years after angioplasty, according to Wenger. She speculates the effectiveness of

The standard stress treadmill test falsely predicts heart disease in as many as half the women tested

angioplasty in women might be limited by their smaller blood vessel size. Angioplasty cannot be performed on blood vessels that are too small, so doctors may not be able to treat all the blockages in women's heart arteries with the procedure, Wenger said.

An alternative therapy to angioplasty is coronary bypass surgery, in which portions of leg veins or an artery in the chest are removed and attached to the heart to provide alternate routes for blood flow, bypassing blocked arteries. Women are two to three times less likely than men to survive this procedure, according to Wenger, perhaps because women are generally older and sicker than men when they have the surgery. If women do survive the operation, however, their five-year survival rate following heart bypass surgery is the same as for men.

A treatment for heart attacks that appears to be equally effective in men and women is "clot-busting" drugs and biologics such as tissue plasminogen activator and streptokinase, both approved by FDA for this purpose. When one of these is given within hours of a heart attack, it can limit the damage to the heart by quickly dissolving the clots blocking heart arteries. However, this treatment may not be as safe in women, who are more likely than men to suffer internal bleeding complications, including hemorrhagic stroke, from these products. Wenger speculates the standard doses, set from testing done mainly in men, are not appropriate for women.

Aspirin and beta-blocker drugs are equally effective in women and men in preventing a second heart attack. But when it comes to other commonly used heart medications, such as those used to dilate blood vessels, "virtually none of these drugs have been studied in women," said Wenger.

The usually smaller body size and higher body-fat content of women, and the hormones generated or taken by women may alter the effects of drugs, according to Ruth Merkatz, Ph.D., a registered nurse formerly with FDA's Office of Women's Health.

Recognizing the problems with prescribing drugs for women that have been analyzed mainly in men, FDA issued a guideline in 1993 that requests women be adequately represented in new drug tests and that the drugs' safety and effectiveness be analyzed for both genders. FDA also set up the Office of Women's Health, to focus on women in clinical trials and develop other measures needed to ensure that most drugs are tested and analyzed in both men and women, said Merkatz. "We won't close the loop and have all the answers tomorrow," she added, "but over the next few

In the first part of a thallium stress test, the patient (here played by a staff member) walks or runs on a treadmill, while Vasken Dilsiban, M.D. (left), monitors her heart rate. After the treadmill, a patient would receive an injection of thallium 201, a radioactive material that allows imaging of the heart muscle. The patient then would rest for two to three hours before another image of the heart muscle is taken in a resting state. A comparison of the two images is used to diagnose coronary artery disease.
(This photo was taken at the Clinical Center of the National Institutes of Health)

PHOTOGRAPH BY RHODA BAER

Each year, nearly twice as many women die from heart disease and stroke as from all forms of cancer combined.

years we'll have much more information on cardiovascular treatments for women."

FDA is also working with academic institutions to further test in women some commonly used cardiovascular drugs already on the market, such as propranolol and quinidine, two heart drugs.

Prevention Tactics Vary

The tricks of the trade for preventing coronary heart disease also vary from men to women. Postmenopausal women may have the option of possibly delaying or preventing the onset of heart disease by taking daily estrogen. Several studies suggest that women who take estrogen during and after menopause have about half the risk of heart attack as women who don't take the hormone. Natural production of estrogen before menopause, some researchers speculate, may explain why women develop heart disease later than men.

Whether estrogen replacement therapy may help delay or prevent heart disease in women, however, remains unproven. Since women selected for estrogen treatment in studies were often healthier, slimmer, and more active than those who didn't receive the hormone therapy, their reduced heart attack risk could have been due to lifestyle characteristics rather than by the estrogen treatment. Because of these uncertainties, FDA has not approved the use of estrogen for prevention of cardiovascular disease.

Use of estrogen after menopause is linked to a greater risk of developing endometrial cancer. To counter that risk, estrogen is often prescribed with the hormone progestin.

Whether this hormone combination also prevents heart disease in women is also unknown. To resolve this question and to prove whether estrogen replacement therapy prevents heart disease in women, the National Institutes of Health has undertaken a randomized clinical trial as part of the Women's Health Initiative. (See "New Attitudes Towards Menopause" in this special issue.)

A mainstay in treating and preventing heart disease in men is a diet low in cholesterol, a fat-like substance carried in the blood and used by the body to build cell walls, sex hormones, and a variety of other vital substances. When too much cholesterol accumulates in the blood, it clogs arteries.

The amount of the two main types of cholesterol found in the blood, however, is key to pinpointing heart disease risk. Cholesterol carried by low-density lipoproteins (LDLs) is more likely to be deposited on artery walls, unlike cholesterol carried by high-density lipoproteins (HDLs), which often is ferried back to the liver where it is processed or removed. High levels of HDL cholesterol and low levels of LDL cholesterol are linked to lower risk of heart disease in both men and women. But HDL levels are a much more powerful predictor of heart disease risk in women than LDL levels, several studies suggest.

A low-cholesterol, low-saturated-fat diet can lower blood cholesterol by more than 15 percent in men. Epidemiological studies of men also found that each 1 percent drop in blood cholesterol was accompanied by a 2 percent drop in the risk of a heart attack.

Research suggests high cholesterol is a risk factor for heart disease in women, too, but experts debate whether women should strive to lower their cholesterol to the levels recommended by the American Heart Association because these levels are based on studies done primarily in men.

A cholesterol-lowering diet in women not only lowers LDL cholesterol, but nearly equally lowers their HDL cholesterol, pointed out John Crouse, M.D., of the Bowman Gray Medical School in North Carolina. Because high HDL levels are so much more protective in women than low LDL levels, lowering total cholesterol may not benefit women and may do more harm than good, he claims. The National Heart, Lung, and Blood Institute is conducting several studies to assess if this is the case.

Like men, however, women can help prevent heart disease by using medications or other measures to stem high blood pressure, losing weight if they are overweight, and not smoking. Both sexes should adhere to a low-fat diet and not consume alcohol if they have high blood levels of triglycerides, a type of fat produced by the liver when alcohol is drunk or when excess calories are taken in.

Scientists are studying whether vitamin E and the vitamin A precursor beta carotene may also help stave off heart disease. Women with a high vitamin E consumption had a 34 percent lower risk of heart disease, according to an epidemiological study by Meir Stampfer, M.D., of Brigham and Women's Hospital in Boston. In the same study of more than 87,000 nurses, those with boosted beta carotene consumption had a 22 percent lower risk of heart disease.

Vigorous aerobic exercise is often touted as a heart disease preventive. But regular walking may be equally effective, according to a small epidemiological study at the Cooper Institute for Aerobics Research in Dallas. Women who walked three miles a day, five days a week decreased their risk of heart disease, even if they took 20 minutes to walk a mile.

Much more research needs to be done, however, to paint a complete and accurate picture of the best ways to prevent, diagnose and treat heart disease in women. Wenger noted that doctors have been looking carefully at heart disease in women for only a few years. "In contrast to 30 years experience looking at it in men—we have a lot of catching up to do," she said. ■

Margie Patlak is a writer in Elkins Park, Pa.

BONING UP ON OSTEOPOROSIS

Consider an insidious condition that drains away bone—the hardest, most durable substance in the body. It happens slowly, over years, so that often neither doctor nor patient is aware of weakening bones until one snaps unexpectedly. Unfortunately, this isn't science fiction. It's why osteoporosis is called the silent thief.

by Carolyn J. Strange

ILLUSTRATION BY JACK PARDUE

There is no cure for osteoporosis, but the onset can be delayed and the severity diminished.

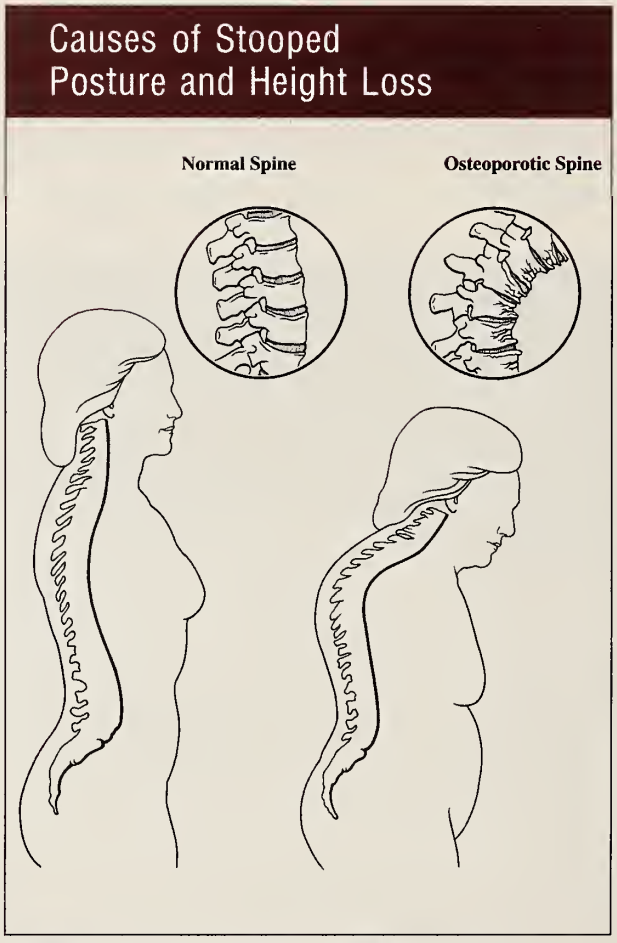
And it steals more than bone. It's the primary cause of hip fracture, which can lead to permanent disability, loss of independence, and sometimes even death. Collapsing spinal vertebrae can produce stooped posture and a "dowager's hump." Lives collapse too. The chronic pain and anxiety that accompany a frail frame make people curtail meaningful activities, because the simplest things can cause broken bones: Stepping off a curb. A sneeze. Bending to pick up something. A hug. "Don't touch Mom, she might break" is the sad joke in many families.

Osteoporosis leads to 1.5 million fractures, or breaks, per year, mostly in the hip, spine and wrist, and costs $10 billion annually, according to the National Osteoporosis Foundation. It threatens 25 million Americans, mostly older women, but older men get it too. One in three women past 50 will suffer a vertebral fracture, according to the foundation. These numbers are predicted to rise as the population ages.

Osteoporosis, which means "porous bones," is a condition of excessive skeletal fragility resulting in bones that break easily. A combination of genetic, dietary, hormonal, age-related, and lifestyle factors all contribute to this condition.

Changing attitudes and improving technology are brightening the outlook for people with osteoporosis. Nowadays, many women live 30 years or more—perhaps a quarter to a third of their lives—after menopause. Improving the quality of those years has become an important health-care goal. Although some bone loss is expected as people age, osteoporosis is no longer viewed as an inevitable consequence of aging. Diagnosis and treatment need no longer wait until bones break.

There is no cure for osteoporosis, and it can't be prevented outright, but the onset can be delayed, and the severity diminished. Most important, early intervention can prevent devastating fractures. The Food and Drug Administration has revised labeling on foods and supplements to provide valuable information about the level of nutrients that help build and maintain strong bones. FDA has also approved a wide variety of products to help diagnose and treat osteoporosis, including several in the last few years.



(SOURCE: NATIONAL OSTEOPOROSIS FOUNDATION, 1993)

The spine is made up of a series of small connected bones called vertebrae (left). Healed vertebral fractures become compressed (flattened) or may mend in a wedge shape. Over time, multiple fractures of the spine can result in stooped posture, a loss of height, and continual pain (right).

Bone Life

Bone consists of a matrix of fibers of the tough protein collagen, hardened with calcium, phosphorus and other minerals. Two types of architecture give bones strength. Surrounding every bone is a tough, dense rind of cortical bone. Inside is spongy-looking trabecular bone. Its interconnecting structure provides much of the strength of healthy bone, but is especially vulnerable to osteoporosis.

"We tend to think of the skeleton as an inert erector set that holds us up and doesn't do much else. That's not true," says Karl. L. Insogna, M.D., director of the Bone Center at Yale School of Medicine, New Haven, Conn. Every bit as dynamic as other tissues, bone responds to the pull of muscles and gravity, repairs itself, and constantly renews itself.

Besides protecting internal organs and allowing us to move about, bone is also involved in the body's handling of minerals. Of the 2 to 4 pounds of calcium in the body, nearly 99 percent is in the teeth and skeleton. The remainder plays a critical role in blood clotting, nerve transmission, muscle contraction (including heartbeat), and other functions. The body keeps the blood level of calcium within a narrow range. When

Osteoporosis leads to 1.5 million fractures, or breaks, per year, mostly in the hip, spine and wrist.

needed, bones release calcium.

A complex interplay of many hormones balances the activity of the two types of cells—osteoclasts and osteoblasts—responsible for the continuous turnover process called remodeling. Osteoclasts break down bone, and osteoblasts build it. In youth, bone building prevails. Bone mass peaks by about age 30, then bone breakdown outpaces formation, and density declines.

The skeleton is like a retirement account, but in our skeletal "account" we can deposit bone only during our first three decades. After that, all we can do is try to postpone and minimize the steady withdrawals. Osteoporosis is the bankruptcy that occurs when too little bone is formed during youth, or too much is lost later, or both.

"You've got to get as much bone as you can and not lose it," Insogna says. "The most important risk factor for osteoporosis is a low bone mass."

"The upper limit of bone mass that you can acquire is genetically determined," says Mona S. Calvo, Ph.D., in FDA's Office of Special Nutritionals. "But even though you may be programmed for high bone mass, other factors can influence how much bone you end up with," she says. (See "Reducing Your Risk.") For instance, men tend to build greater bone mass, which is partly why more women face osteoporosis.

But there's another reason. With the decline of the female hormone estrogen at menopause, usually around age 50, bone breakdown markedly increases. For several years, women lose bone two to four times faster than they did before menopause. The rate usually slows down again, but some women may continue to lose bone rapidly. By age 65, some women have lost half their skeletal mass. Because the changes at menopause increase a woman's risk, many physicians feel it's a good time to measure a woman's bone density, especially if she has other risk factors for osteoporosis.

"The best way to gauge a woman's risk for osteoporotic fracture is to measure her bone mass," says Insogna.

Routine x-rays can't detect osteoporosis until it's quite advanced, but other radiological methods can. FDA has approved several kinds of devices that use various methods to estimate bone density. Most require far less radiation than a chest x-ray. Doctors consider a patient's medical history and risk factors in deciding who should have a bone density test. The method used is often determined by the equipment available locally. Readings are compared to a standard for the patient's age, sex and body size. Different parts of the skeleton may be measured, and low density at any site is worrisome.

Bone density tests are useful for confirming a diagnosis of osteoporosis if a person has already had a suspicious fracture, or for detecting low bone density so that preventative steps can be taken.

"There's a profound relationship between bone mass and risk of fracture," says Robert Recker, M.D., director of the Osteoporosis Research Center at Creighton University, Omaha, Neb.

Readings repeated at intervals of a year or more can determine the rate of bone loss and help monitor treatment effectiveness. However, estimates are not necessarily comparable between machine types because they use different measurement methods, cautions Joseph Arnaudo, in the Center for Devices and Radiological Health. "You always want to go back to the same machine, if you can," he says.

Another new test provides an indicator of bone breakdown. FDA approved in 1995 a simple, noninvasive biochemical test that detects in a urine sample a specific component of bone breakdown, called NTx. Clinical labs can get results in about 2 hours. The NTx test, marketed as Osteomark, can help physicians monitor treatment and identify fast losers of bone for more aggressive treatment, but the test may not be used to diagnose osteoporosis.

Expanding Treatment Options

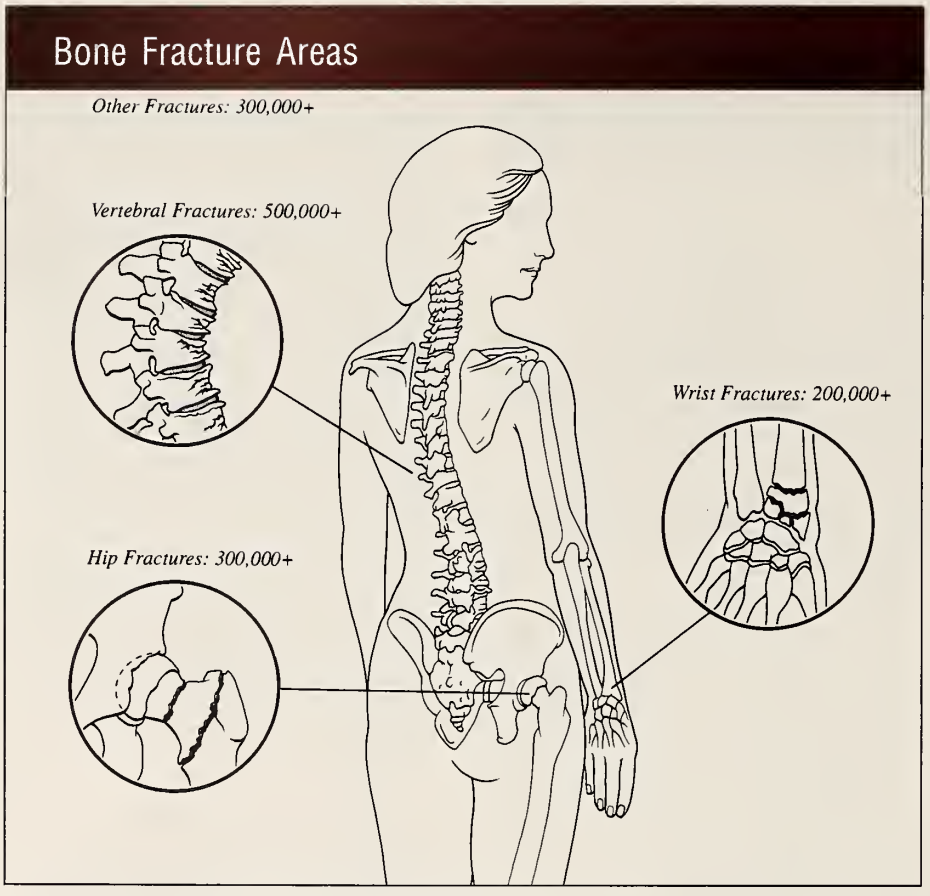
Physicians and patients now have more treatment options than ever. Under FDA guidelines, drugs to treat osteo-

To Learn More

For more information, contact:

- National Osteoporosis Foundation, 1150 17th St., N.W., Suite 500, Washington, DC 20036; (202) 223-2226; World Wide Web: *http://www.nof.org/*. For locations of your nearest bone density testing sites, call (800) 464-6700.
- Osteoporosis and Related Bone Diseases National Resource Center (ORBD-NRC); (800) 624-BONE; TDD: (202) 223-0344.
- Older Women's League (OWL), 666 11th St., N.W., Suite 700, Washington, DC 20001; (202) 783-6686.
- North American Menopause Society, c/o University Hospitals of Cleveland, Department of Obstetrics and Gynecology, 11100 Euclid Ave., Suite 7024, Cleveland, OH 44106; (216) 844-8748; World Wide Web: *http://www.menopause.org/*.
- American Association of Retired Persons (AARP), 601 E St., N.W., Washington, DC 20049; (202) 434-2277; World Wide Web: *http://www.aarp.org/*.

Late in 1996, FDA approved the first nonhormonal treatment for osteoporosis.



(SOURCE: NATIONAL OSTEOPOROSIS FOUNDATION, 1993)

Each year, osteoporosis leads to 1.5 million bone fractures, including more than 500,000 vertebral fractures, 300,000 hip fractures, 200,000 wrist fractures, and 300,000 fractures of other bones.

porosis must be shown to preserve or increase bone mass and maintain bone quality in order to reduce the risk of fractures. "We want to be sure that the bone is normal or stronger than it was," says Gloria Troendle, M.D., deputy director of the division of metabolism and endocrine drug products in FDA's Center for Drug Evaluation and Research.

Before 1995, the only choices were the hormones estrogen and calcitonin. While enthusiasm for new weapons against osteoporosis is warranted, one of the old ones is still the top choice.

"Estrogen remains the first thing that women should consider," says Insogna, because the hormone not only helps prevent osteoporosis, but also protects against heart disease.

"If you think about what's missing at menopause, it's the hormones," says Paula Stern, Ph.D., a pharmacologist at Northwestern University Medical School, Chicago, Ill.

Estrogen replacement therapy is the best prevention for the drop in bone mass at menopause, and there are more ways to take it than ever. But it's not for everyone. Because estrogen increases the risk of certain cancers and other diseases, taking it may not be appropriate, or it may be given in combination with another female hormone, progesterone, which can also cause undesirable side effects. A woman and her doctor need to carefully weigh the risks and benefits. According to the National Osteoporosis Foundation, a woman's risk of developing a hip fracture is equal to her combined risk of developing breast, uterine and ovarian cancer.

Women who can't or don't want to take hormones—some 30 to 50 percent—have other treatment avenues. For example, calcitonin treatment became much easier when FDA approved a nasal spray in the summer of 1996. Calcitonin, one of the hormones responsible for regulating the level of calcium in the blood, inhibits osteoclasts, the bone dissolvers. The drug, marketed as Miacalcin, is a potent, synthetic version of the hormone, and has been shown to slow and reverse bone loss. The stomach quickly destroys the drug, so before the spray was available, calcitonin had to be injected every day or two.

Later in 1996, FDA approved the first nonhormonal treatment for osteoporosis. Alendronate, marketed as Fosamax, falls within a class of drugs called bisphosphonates, which hinder bone breakdown remodeling sites by inhibiting osteoclast activity. In clinical trials lasting three years, alendronate increased the bone mass as much as 8 percent and reduced fractures as much as 30 to 40 percent, depending on skeletal site. Lengthier studies are ongoing.

To avoid damage to the esophagus, Fosamax should be taken according to the instructions. These instructions include taking the drug in the morning upon awaking and at least half an hour before eating. The drug should be taken with 6 to 8 ounces of water, and the person should remain upright for half an hour after taking it. Fosamax should not be taken by people who cannot stand or sit upright or who have disorders that

prevent esophageal emptying into the stomach.

"All the drugs approved so far are things that just stop bone turnover. They're not really stimulating more bone production," says Troendle.

Bone mass increases because even though osteoclasts can't start new remodeling sites, osteoblasts continue filling in existing cavities. Increases in bone mass are most pronounced in the first year or two after treatment begins, then taper off. Any gain is helpful, even if it doesn't continue, because increases in bone mass help reduce fracture risk. But experts would like to encourage even greater gains.

Fluoride, known for fighting dental cavities, stimulates bone building, but early studies in osteoporosis patients found that the structure of the new bone was abnormal and weaker than normal bone. Gastrointestinal side effects were also a problem. Investigators are working to find a formulation and dosage regimen that will result in building normal bone.

Drugs Not Enough

Calcium and vitamin D supplements are an integral part of all treatments for osteoporosis. Everyone should make sure they get enough of these two nutrients, but especially women and others at risk for osteoporosis. Attention to diet and exercise are important not only for treatment, but also for prevention.

"If you go to the doctor and get a prescription, and that's all you do, you're probably not going to be helped very much," Recker says.

Calcium intake is critical, and those who need it the most—younger women and girls—don't get enough. (See "Calcium (Ac)Counts.") But calcium alone can't build bone. Without vitamin D, calcium isn't sufficiently absorbed. Most people get enough vitamin D because skin produces it in sunlight. But people confined indoors who have a poor diet—which includes many older Americans—or who live in northern latitudes in winter may be deficient.

A lifelong habit of weightbearing exercise, such as walking or biking, also helps build and maintain strong bone. The greatest benefit for older people is that physical fitness reduces the risk of

Calcium and vitamin D supplements are an integral part of all treatments for osteoporosis.

Calcium (Ac)Counts

Your skeletal calcium bank has to last through old age. Frequent deposits to this retirement account should begin in youth and be maintained throughout life to help minimize withdrawals. Most women get much less calcium than they need—as little as half.

Nutritionists recommend meeting your calcium needs with foods naturally rich in calcium. Adequate calcium intake in childhood and young adulthood is critical to achieving peak adult bone mass, yet many adolescent girls replace milk with nutrient-poor beverages like soda pop. "Bone health requires a lot of nutrients and you're likely to get most of them in dairy products," says Connie Weaver, Ph.D., who heads the department of food and nutrition at Purdue University, Indiana. "They're a huge package rather than just a single nutrient." With so many low-fat and nonfat dairy products available, it's easy to make dairy foods part of a healthy diet. People who have trouble digesting milk can look for products treated to reduce lactose. A serving of milk or yogurt contains about 350 milligrams (mg) of calcium. Fortified products have even more.

"People who don't consume dairy foods can meet their calcium needs with foods that are fortified with calcium, such as orange juice, or with calcium supplements," says Mona S. Calvo, Ph.D., in FDA's Office of Special Nutritionals. Other good sources of calcium are broccoli and dark-green leafy vegetables like kale, tofu (if made with calcium), canned fish (eaten with bones), and fortified bread and cereal products.

Nutrition labels can help you identify calcium-rich foods. But keep in mind that the label value is a guideline based on a FDA's Daily Value for calcium, which is 1,000 mg, and your calcium needs may be greater, Calvo says.

What about too much calcium? As much as 2,000 mg per day seems to be safe for most people, but those at risk for kidney stones should discuss calcium with their doctors. Calcium is critical, but even a high intake won't fully protect you against bone loss caused by estrogen deficiency, physical inactivity, alcohol abuse, smoking, or medical disorders and treatments. ■

—C.J.S.

Reducing Your Risk

A host of factors can affect your chances of developing osteoporosis. The good news is that you control some of them. Even though you can't change your genes, you can still lower your risk with attention to certain lifestyle changes. The younger you start, and the longer you keep it up, the better. Here's what you can do for yourself:

- Be sure you get enough calcium and vitamin D.
- Engage in regular physical activity, such as walking.
- Don't smoke.
- If you drink alcohol, do so in moderation.

A sedentary lifestyle, smoking, excessive drinking, and low calcium intake all increase risk. Although coffee has been suspected as a risk factor, studies so far are inconclusive.

Other factors are beyond your control. Being aware of them can provide extra motivation to help yourself in the ways you are able, and aids you and your doctor in health-care decisions. These risk factors are:

- being female: Women have a five times greater risk than men.
- thin, small-boned frame
- broken bones or stooped posture in older family members, especially women, which suggest a family history of osteoporosis
- early estrogen deficiency in women who experience menopause before age 45, either naturally or resulting from surgical removal of the ovaries
- estrogen deficiency due to abnormal absence of menstruation (as may accompany eating disorders)
- ethnic heritage: White and Asian women are at highest risk; African American and Hispanic women are at lower, but significant, risk.
- advanced age
- prolonged use of some medications, such as excessive thyroid hormone; some antiseizure medications; and glucocorticoids (certain anti-inflammatory medications, such as prednisone, used to treat conditions such as asthma, arthritis and some cancers).

Risk factors may not tell the whole story. You may have none of these factors and still have osteoporosis. Or you may have many of them and not develop the condition. It's best to discuss your specific situation with your doctor. ■

—C.J.S.

fracture, because better balance, muscle strength, and agility make falls less likely. Exercise also provides many other life-enhancing psychological and cardiovascular benefits. Increased activity can aid nutrition, too, because it boosts appetite, which is often reduced in older people. The biggest reason older people don't get enough calcium, Recker says, is that they simply don't eat much.

"The truth is, you don't have to do very much to get most of the benefits of exercise," Recker says. He suggests 30 minutes of brisk walking five days a week. Add a little weightlifting, and that's even better. It's always smart to ask your doctor before starting a new exercise program, especially if you already have osteoporosis or other health problems.

Brighter Horizons

"A number of new things seem to be in the offing, eventually to come to us, and we're looking forward to getting some additional treatments for osteoporosis," says Troendle.

Uses of existing drugs may be broadened. Early drug trials are often conducted with patients who have severe disease, often after a fracture has occurred or bone loss is quite serious. Some studies under way are testing to see if certain drugs are effective in less severe cases, if they can be started sooner, or used in combination.

The search for bone-building drugs continues. Some naturally occurring bone-specific growth factors have been identified and their use as drugs is being investigated. "The way I visualize the ideal future is that we'll be able to give Drug X that builds up bone to where it's stronger and the risk of fracture is no longer present, then Drug Y maintains it by preventing breakdown," says Stern.

In the realm of devices, researchers are exploring the use of ultrasound to assess bone health. Such tests would eliminate radiation exposure and probably cost less. The study of risk factors also continues. "We consider that to be the research that has the greatest public health significance," says Sherry Sherman, Ph.D., of the National Institute on Aging. The institute has begun the Study of Women's Health Across the Nation, a large-scale national examination of the health of women in their 40s and 50s. Researchers expect to learn a great deal about the factors affecting women's health during these transitional years and beyond. Studies of genetics, biochemical markers, and life habits are already turning up new insights.

Osteoporosis has been described as an adolescent disease with a geriatric onset, highlighting the importance of beginning to take steps—in exercise and diet—early in life to reduce its disabling impact in later years. ■

Carolyn J. Strange is a science and medical writer living in Northern California.

WOMEN And AIDS

by Marian Segal

Infections with HIV, the virus that causes AIDS, have been rising faster in women than in men. The percentage of female infected adults and adolescents increased steadily, from 7 percent in 1985 to 18 percent in 1995. And although total deaths from AIDS declined by 12 percent overall in the first half of 1996, deaths among women with AIDS rose by 3 percent during the same period.

The disease disproportionately affects minority women. Although African-American and Hispanic women make up 21 percent of the country's female population, they account for about 75 percent of women diagnosed with AIDS. This does not mean that a person is at risk simply by being a member of a racial or ethnic minority group; rather, it reflects the higher numbers of minority populations in communities with a high incidence of HIV infection.

In this country, most women who now have AIDS became infected with HIV by injecting illegal drugs. But the rate of infection through heterosexual transmission has been rising dramatically. Of 13,996 women whose AIDS cases were reported between July 1995 and June 1996, 36 percent were infected through injection drug use and 40 percent through sex.

The Centers for Disease Control and Prevention reports that, "Many women in the United States are unaware they are at risk for HIV infection, and HIV-infected women often remain undiagnosed until the onset of AIDS or until a perinatally infected child [infected before or during birth] becomes ill."

What You Don't Know Can Hurt You

A woman may not realize she is at risk for HIV. For example, she may not know her sex partner uses or has used intravenous drugs or is bisexual or has had at-risk sex partners in the past. She may disregard symptoms that could serve as warning signals and therefore, not seek testing or treatment.

"Delayed diagnosis affects survival," says Theresa Toigo, associate commissioner for the Office of AIDS and Special Health Issues in the Food and Drug Administration. "The late diagnosis of women has contributed to past reports that women's survival time is shorter than men's. It's not." If a woman is diagnosed at the same point in the disease as a man, her survival is, on the average, the same. But most HIV-infected women are from poor populations with poor access to health care, whereas many men with HIV are more affluent gay men from areas with better medical resources.

"Probably the biggest contribution that can be made to the survival of someone with HIV is to get them into early treatment," says Toigo.

Based on experience with the gay male population, it appears that education and awareness are important in stemming the tide of HIV infection. Early in the AIDS epidemic, gay men—who were then the hardest hit group—organized and conducted an extensive education program that proved effective in bringing many gay men into clinics for testing and treatment.

Federal, state, local, and nongovernment agencies are working together and individually to step up prevention efforts, improve diagnostic and treatment services, and establish community-based health education and risk-reduction programs for diverse populations, including gay and bisexual men, prostitutes, injection drug users, heterosexuals with multiple sex partners, women at risk, homeless people, and youth in high-risk situations, such as runaways and youngsters in shelters or detention centers.

President Clinton in 1993 established the Office of AIDS Policy to coordinate all federal-level efforts against the epidemic. In addition, the National Task Force on AIDS Drug Development was established by the Secretary of Department of Health and Human Services to identify barriers to the rapid development of therapies for the treatment of AIDS. The task force has provided an opportunity for members of affected communities, the pharmaceutical industry, academia, and government agencies to engage in frank discussions about removing obstacles to AIDS drug development. These discussions have been reinforced by the President's Summit on AIDS in December of 1995 and subsequent meetings of the President's Advisory Council on AIDS, as well as Vice President Gore's meetings with the pharmaceutical industry.

It's expected that FDA's approval in 1996 of two blood tests will result in earlier diagnosis of HIV infection, especially among women and minorities. A home test kit, available over the counter, enables a person to obtain a blood sample at home and then send it, with identity protected, to a lab for analysis. Counseling is provided as part of the test system. Orasure Western blot is a laboratory test that doesn't require a blood sample. Rather, it requires a tissue sample that can be collected from between the gum and cheek.

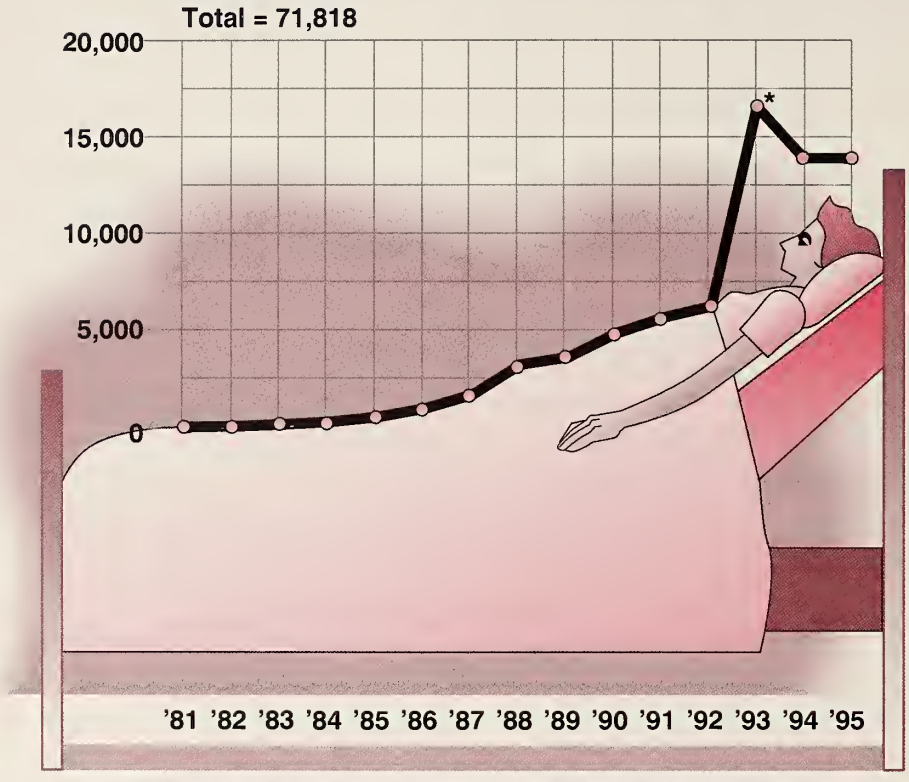
Drug Labels Provide Warning

To help increase awareness about the most common early indicator of HIV infection in women—recurrent vaginal candidiasis (yeast infections)—FDA in October 1992 required manufacturers of over-the-counter drugs for these infections to include a new label warning on their products.

The warning states that frequent vagi-

AIDS Increases Among Women and Teenage Girls

Cases Reported Among Females 13 and Older



***On Jan. 1, 1993, the definition of AIDS was broadened. Earlier cases that fit this expanded definition but had never been reported were included in the reports for 1993 and accounted for most of the sharp jump in reported cases for that year.**

(Source: Centers for Disease Control and Prevention)

nal yeast infections (recurring within a two-month period)—especially those that don't clear up easily with proper treatment—may be the result of serious medical conditions, including HIV infection, and advises women with these symptoms to see their doctors. (Recurrent yeast infections also may result from hormonal changes or use of oral contraceptives or antibiotics, as the label already noted.) Examples of over-the-counter preparations that must carry these warnings are Monistat-7 (miconazole nitrate); Gyne-Lotrimin, Mycelex-7, and FemCare (clotrimazole); Femstat 3 (butoconazole nitrate); and generic versions of these products. Manufacturers of oil-containing or oil-based vaginal creams for treating yeast infections and other vaginal infections must also warn patients not to rely on latex barrier contraceptives, such as latex condoms or diaphragms, when using their products. The cream may cause the latex to weaken or break.

Other illnesses and infections in women that should prompt concern about possible HIV infection include pelvic inflammatory disease (PID), cervical dysplasia (precancerous changes in the cervix), yeast infections of the mouth and throat, and any sexually transmitted disease, such as genital ulcers and warts and herpes infection.

In February 1995, FDA published a proposed rule in the *Federal Register* to require manufacturers of over-the-counter spermicides to submit data showing their products are effective as contraceptives. The agency also strongly encouraged manufacturers to evaluate these products for prevention of sexually transmitted diseases, including HIV. Though the administrative record for this rule originally closed on April 3, 1996, after discussions with industry, FDA reopened the record, with the comment period ending March 3, 1997.

AIDS Definition Revised

A doctor diagnoses AIDS when an HIV-infected person develops one of several infections or diseases specified by CDC in its "AIDS surveillance case definition." These illnesses include PCP (*Pneumocystis carinii* pneumonia), Kaposi's sarcoma (a type of cancer), toxoplasmosis, and others. As knowledge about HIV and AIDS has grown over the years, CDC has expanded its definition to include additional AIDS-defining illnesses. In January 1993, CDC added cervical cancer, along with pulmonary tuberculosis and recurrent pneumonia, to the list of AIDS-indicator illnesses in HIV-infected people.

The revised AIDS definition also includes all HIV-infected people with severe CD4 cell depletion (less than 200 CD4 cells per cubic millimeter). CD4 cells are critical immune system cells that number from about 800 to 1,000 in a healthy person.

According to the earlier definition, a person with a very low CD4 count but no AIDS-defining illness was not included in the case definition of AIDS.

Treatment

Available data suggest that drugs used to treat HIV work similarly in men and women. These drugs are usually grouped by the way they fight the virus. When this special issue went to press, approved agents included:

Reverse Transcriptase Inhibitors

- *Non-nucleosides:*
  Viramune (nevirapine)
- *Nucleosides:*
  Retrovir (zidovudine, also known as AZT)
  Videx (didanosine, also known as DDI)
  Hivid (zalcitibine, also known as DDC)
  Zerit (stavudine, also known as d4t)
  Epivir (lamivudine, also known as 3TC)

Protease Inhibitors

- Invirase (saquinavir)
- Norvir (ritonavir)
- Crixivan (indinavir)

Mother and Child—The HIV Connection

According to the Surgeon General's 1993 report on HIV infection and AIDS, about 1 in 4 of babies born to HIV-infected women at that time became infected before or during birth. Scientists have been trying for some time to discover what influences whether or not a child will be affected.

No one is certain when viral transmission occurs. Possibilities include: during childbirth, from exposure to maternal blood or vaginal fluids; or earlier in pregnancy, when there may be a mixing of blood or passage of the virus across the placental wall.

In August 1994, FDA approved Retrovir (zidovudine, or AZT) for use in preventing transmission of HIV from infected pregnant women to their babies. Approval was based on results of a federally sponsored study showing that the risk of transmission to newborns from infected mothers is significantly reduced in women receiving zidovudine during pregnancy. Since its approval, AZT has been observed to reduce HIV transmission to infants from 25 percent in untreated mothers to 8 percent in those treated with AZT.

In response to reports of a study suggesting that very high daily doses of AZT increased certain types of cancer in baby mice, an independent NIH advisory panel unanimously agreed in January 1997 that the benefits of HIV-infected pregnant women taking AZT outweigh the theoretical concerns raised by the study. There are no reports of any human child developing cancer after AZT treatment and it is unclear whether the mouse study results apply to humans. The committee also recommended that pregnant HIV-infected women be told about the study before being given the drug and emphasized the need for careful long-term follow-up of all children born to pregnant women who received AZT.

To gain the most benefit from AZT therapy, women need to be diagnosed early in the course of their infection and before or early in the pregnancy. To this end, the Public Health Service recommended HIV counseling and voluntary testing of all pregnant women in the United States.

Apart from the timing of transmission, studies suggest that the likelihood of the child becoming infected may correlate with the mother's health during the pregnancy or birth. In the June 9, 1993, *Journal of the American Medical Association,* Michael E. St. Louis, M.D., and his colleagues reported that a baby is more likely to become infected if the mother is in the very earliest stage of infection (when the virus is thought to be abundant) or in an advanced stage of disease, or if the membrane surrounding the placenta is inflamed.

A child can also become infected after birth through breast-feeding.

The national Centers for Disease Control and Prevention had received reports of more than 6,000 cases of AIDS in children infected before or during birth or through breast-feeding, as of Dec. 31, 1995. Not surprisingly, experts predict that as more women of childbearing age become infected, the number of infected children will also rise. A disturbing prospect under any circumstances, the significance of this projection is most poignant for minorities in New York City, where AIDS is already the leading cause of death in Hispanic children 1 to 4 years of age and the second leading cause of death for African American children of the same ages. ■

—M.S.

Data that became available in 1996 has given new hope to people with HIV infection. For the first time, combinations of new and older agents and the availability of the newer monitoring techniques have demonstrated that therapies can dramatically reduce the amount of virus measurable in the blood. This is often associated with improved health.

The AIDS Clinical Trials Information Service (ACTIS) can provide current information on federally and privately sponsored HIV and AIDS drug and vaccine clinical trials, free customized searches of national clinical trials and drug databases, and confidential, personalized assistance from English- and Spanish-speaking health specialists. (See "Information Sources.")

Certain infections may be more severe or prolonged or occur more frequently in people with HIV infection, and so may require different forms of therapy. For example, some doctors may prescribe oral antifungals for vaginal yeast infections in HIV-infected women instead of the commonly used vaginal products.

Similarly, PID, syphilis, gonorrhea, and genital warts may be harder to treat in HIV-infected women. PID, which normally produces fever and pain, may go unnoticed in an HIV-infected woman because her body hasn't been able to mount the immune response that causes these symptoms. Therefore, her infection may worsen for quite some time before she gets medical help.

Syphilis, effectively treated with penicillin in an otherwise healthy woman, may require higher doses or different drugs and have a lower cure rate in an HIV-infected person. Genital warts, which are associated with cervical cancer and obstruction of the urinary bladder, may require laser surgery.

Cervical dysplasia, too, can lead to cervical cancer. In HIV-infected women, cervical dysplasia appears to be more common and may progress more quickly to cervical cancer than in uninfected women. For these reasons the American College of Obstetrics and Gynecology and most practitioners recommend that women with HIV have Pap tests twice a year to make sure cancer is detected and treated early.

The federal government, in June 1997, recommended that all people with AIDS receive a combination treatment of three antiviral drugs, including one protease inhibitor. It also recommended that most people with early HIV infection also receive the combination therapy.

Prevention

Armed with knowledge about risks and prevention, women can do much to protect themselves from HIV infection. According to CDC, as of December 1995, about half of all reported cases of AIDS in adult and adolescent women were due to injection drug use, and about another third resulted from heterosexual transmission. Transfusion of blood or blood products accounted for another 5 percent.

The risk of transmission of HIV from transfused blood has been substantially reduced since 1985, due to the HIV-1 antibody and antigen test kits to screen blood donors for HIV-1. Antigens, which are the virus' own proteins, can be detected about a week earlier than antibodies. In addition, blood products used to treat hemophilia have been treated with cryoprecipitate.

The most important risks for women are using injection drugs, having unprotected sex with someone who uses or has used injection drugs, and having unprotected sex with a man who has had sex with another man. Having multiple sex partners also increases risk of infection.

Safer Sex

In the United States, the odds of a woman becoming infected from a man are much greater than the reverse. In one recent study of 379 couples, researchers found a 1 percent rate of female-to-male transmission of HIV, compared with a 20 percent rate of male-to-female transmission.

"The surest way to protect yourself against HIV infection and other STDs is not to have sex at all, or to have sex only with one steady, uninfected partner," states the Surgeon General's 1993 report on HIV infection and AIDS. The following advice for women who are not in such a relationship and engage in sex:

- *The man must wear a condom every time you have sex, whether it's vaginal, anal or oral, and must use it properly.*
- Use a new condom for every act of intercourse.
- Use condoms made of latex rubber. Natural membrane condoms have microscopic holes the virus may be able to pass through.
- Put the condom on as soon as the penis becomes erect and remove it promptly after ejaculation.
- Use only water-based lubricants. Oil-based lubricants (such as petroleum jelly, cold cream, baby oil, and cooking shortening) weaken the condom and can cause it to break.

Most failures with condoms are user failures—failure to use the condom at all or failure to use it correctly. Condoms also provide protection from STDs such as syphilis, gonorrhea, chlamydia, herpes, and genital warts. This is important for preventing HIV infection as well, because sores from these diseases provide easier access for the virus to enter the blood stream. People with STDs should consider themselves at risk for HIV.

Even women infected with HIV should have their partners use a condom to protect themselves from infection by other sexually transmitted viruses or bacteria and to help protect against infection from another strain of HIV. Many researchers believe that infections with more than one strain of HIV may lead to more rapid progression of disease or to introduction of resistant forms of the virus.

Do not rely on other forms of contraception for protection against HIV.

In April 1993, FDA announced that birth control pills, implantable contraceptives such as Norplant, injectable contraceptives such as Depo-Provera, IUDs, and natural membrane condoms must carry labeling that states these products are intended to prevent pregnancy but do not protect against HIV infection and other STDs. FDA has approved the marketing of male condoms made of polyurethane as effective in preventing STDs, including HIV. The polyurethane condom is an alternative for individuals allergic to latex.

The Reality Female Condom, made from polyurethane, may afford some

Information Sources

General Information

CDC National AIDS Hotline

- English service (1-800) 342-AIDS (2347)
  (7 days a week, 24 hours a day)
- Spanish service (1-800) 344-7432
  (7 days a week, 8 a.m. to 2 a.m. Eastern time)
- TDD service for the deaf (1-800) 243-7889
  (Monday through Friday, 10 a.m. to 10 p.m. Eastern time)

CDC National AIDS Clearinghouse (1-800) 458-5231

P.O. Box 6003
Rockville, MD 20849-6003

- TTY/TDD (1-800) 243-7012
  (Monday through Friday, 9 a.m. to 7 p.m. Eastern time)
- World Wide Web: *http://www.cdcnac.org/nacpubs.html*

HIV AIDS Treatment Information Service (1-800) 448-0440

P.O. Box 6303
Rockville, MD 20849-6303

- TDD service for the deaf (1-800) 243-7012
  (Monday through Friday, 9 a.m. to 7 p.m. Eastern time)

National Institute on Drug Abuse Hotline

- English service (1-800) 662-HELP (4357)
- Spanish service (1-800) 66-AYUDA (29832)

Status of U.S. HIV Clinical Trials

AIDS Clinical Trials Information Service (1-800) TRIALS-A (874-2572)

- TTY/TDD (1-800) 243-7012
- International (1-301) 217-0023
- Fax (1-301) 738-6616
  (Monday through Friday, 9 a.m. to 7 p.m. Eastern time)
- World Wide Web: *http://www.actis.org/*

For a copy of the 1993 *Surgeon General's Report to the American Public on HIV Infection and AIDS,* call (1-800) 342-AIDS.

protection against STDs, but it is not as effective as latex condoms for men. In approving the device, FDA required the labeling to indicate that for "highly effective protection" against STDs, it is important to use latex condoms for men. The male and female condom *cannot* be used at the same time. If used together, both products will not stay in place.

In addition, there is no evidence that diaphragms, or spermicides protect against HIV transmission.

Drug Use

Any illegal drug use puts a person at risk for HIV. An HIV-infected person who uses injection drugs and shares needles can pass the virus to someone else through tiny amounts of blood that remain in the needle or syringe.

Women who use non-injection drugs, especially crack and other forms of cocaine, also increase their risk for HIV because they may engage in risky sexual activity. Drug and alcohol use may cause a person to be less careful about choice of sex partners or to neglect to use a condom.

The Surgeon General's report advises:

- If you use illegal drugs, try to get treatment to help you stop.
- If you can't stop injecting illegal drugs, never share your equipment with anyone or reuse equipment used by someone else. HIV may be found in any equipment used to inject drugs, including needles, syringes, cotton, and "cookers" (containers used to mix and heat drugs for injection).
- If you share or reuse injection equipment, clean and disinfect it between uses by flushing needles and syringes with water until they are visibly clear of blood and debris and then completely filling the equipment several times with full-strength household bleach. The longer the syringe is full of fresh bleach, the more likely the virus will be killed. (Some suggest the syringe should be full of bleach for at least 30 seconds.) After each bleach filling, rinse the syringe and needle several times by filling with clean water.
- Cleaning injection equipment decreases the potential for infection but does not guarantee the equipment is sterile or all virus is killed. If you cannot stop injecting drugs, it's best to use only sterile needles and syringes.

More Work to Be Done

AIDS and other illnesses due to HIV infection are the fourth leading cause of death in American women aged 25 to 44. In New York and New Jersey, it's the number one cause of death for women in this age group.

"FDA is concerned about this trend," says Toigo. The agency is meeting with women's groups, professional groups, and activists representing women with AIDS in cities and rural areas, among minorities and underserved populations.

The meetings provide a forum for the agency to hear the concerns of those in the trenches and work with the groups to try to contain an epidemic that is increasingly affecting women, especially among minorities. ■

Marian Segal is a member of FDA's public affairs staff. Judith Levine Willis also contributed to this article.

Equality In Clinical Trials

Drugs and Gender

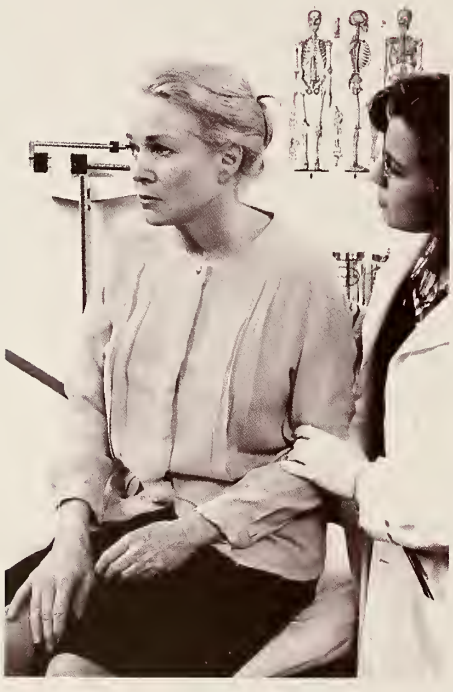
by Judith Levine Willis

Women woke up almost twice as fast from anesthesia as men in a study reported at the annual meeting of the American Society of Anesthesiologists in October 1996. In another recent study, the class of painkillers called kappa opioids seemed to work about twice as well for women as for men. These are but two of a growing number of clinical studies providing new information about possible differences in ways women and men respond to drugs.

Reporting on the anesthesia study, one of the researchers, Peter S. Glass of Duke University Medical Center, said the gender finding emerged unexpectedly during a study of how management of anesthetic drugs during surgery influences recovery time from general anesthesia. The study included 300 people. Women took an average of seven minutes to emerge from anesthesia, while men took 13. The difference occurred independently of differences in body weight.

In the painkiller study, according to a report published in the November 1996 issue of *Nature Medicine*, women having wisdom teeth removed had a better and longer response to these drugs than men, even when factors such as body size and menstrual cycle were considered.

Until recently, women were not routinely included in many human trials to determine whether drugs are safe and effective. The reason usually given was that excluding women protected them, since there was often no way to be sure that a woman was not pregnant or that the drug might not cause some problem



that might interfere with future pregnancies. In addition, it was thought that women's hormonal cycling or other factors peculiar to being female might constitute variables that could skew trial results.

However, over the last several years, research has accumulated indicating that drug results from male-only trials may not apply equally to women, or may not give data on effects important to women. At one time, researchers thought most of the differences between the way men and women reacted to drugs might be attributed to differences in height, weight and hormones. This meant, for example, that simply because most men weigh more than most women, most men would be able to tolerate higher doses of medications without side effects.

Today many scientists think it's far more complicated. For example, the liver may be different enough in men and women to account for at least part of why most women seem to metabolize drugs differently than men. And in the case of pain relief, there may be gender differences in pain tolerance and differences in the way each gender responds to various pain medications.

The rising recognition of these and other gender factors has brought changes in the way the Food and Drug Administration asks firms to test drugs and in the data the agency asks them to provide.

For example, in September 1995 FDA proposed to amend its investigational and new drug regulations to require drug sponsors to include data about gender, as well as age and race. The proposal does not require manufacturers to conduct additional studies. Rather, the manufacturers would simply provide information previously gathered in a new, more useful, format.

FDA suggested changes of this nature in 1993 as a revision to a 1977 Guideline, "General Considerations for the Clinical Evaluation of Drugs," after the agency found that few women were included in the earliest stages of drug clinical trials. In addition, the agency found that there had been little study of the effects on drug action of such factors as the menstrual cycle, menopause, and hormone use. The 1993 guideline left gender analysis voluntary; it was not a requirement.

Subsequent studies by FDA and the

General Accounting Office have shown that women are often included in later phases of clinical trials, and are included in proportions similar to the proportion of women who have the condition the drug is being tested for. But FDA believes that inclusion alone is not enough. What is needed, in addition, is an effort to use data from the trials to discover potential gender differences.

Impact of HIV

Rachel Behrman, M.D., supervisory medical officer in FDA's division of antiviral drug products, says the issues surrounding these changes were brought to the forefront by efforts to treat HIV (the virus that causes AIDS) in women.

"The guidelines always provided that women with serious or life-threatening diseases could obtain an experimental drug in early phases of testing," says Behrman. "What's new is that now we're saying to drug manufacturers, 'Not only do we recommend that you study it in women, we may insist that you do so, if it's going to be used by women who have serious and life-threatening diseases.' "

She explains that because of the urgent need, drug testing for HIV is on a fast track, with condensed stages of controlled studies and, frequently, fewer people in them.

"Since the process moves so quickly, extensive clinical data collected over a long period of time often are not available," she says. "You need to know as soon as possible, for example, what adverse effects occur that might be dose-dependent, and work up those differences early in the drug development program. You don't want to wait for later stages of testing to begin to define dosage adjustments for men and women."

Many researchers feel the reason for including women in any phase 1 drug trial—regardless of the seriousness of the disease—should be to provide important data about the drug. This data includes whether women in general absorb, metabolize or excrete the drug differently from men, or have different reactions to the drug.

Early in the AIDS epidemic, very few women with HIV were included in studies. But their numbers are increasing. According to the National Institute of Allergy and Infectious Diseases (NIAID), in 1995 women accounted for 16.2 percent of adult participants in the AIDS Clinical Trials Group, the institute's largest clinical trials network. That percentage is up from 7 percent in 1988 and 8.4 percent in 1991.

In a study by FDA's Behrman, Kimberly Struble, Theresa Toigo, and Debra Birkrant, 136 of 156 clinical studies of HIV treatment conducted between 1988 and 1994 enrolled women. And, even in the 20 trials that did not include women, enrollment of women—including those of childbearing age—was permitted. Enrollment of women in the other trials ranged up to 64 percent, with a mean of 11.6 percent.

Some HIV studies include only women. Better information on the length of survival and quality of life in HIV-infected women are research goals of the Women's Interagency HIV Study, conducted by the Centers for Disease Control and Prevention and NIAID. This large-scale study is designed to identify clinical signs of HIV infection in women, describe how the immune system declines, and look for factors that can affect the progression of the disease. It will also examine factors influencing women's access to health care.

Other NIAID-sponsored studies center on pregnancy and HIV. They are designed to examine the effect of antiviral drug treatment on both the mother and fetus, the influence of HIV on pregnancy, and the effects of pregnancy on the course of HIV infection. In addition, two experimental vaccines are being tested in pregnant women who are infected with HIV but are otherwise healthy. Phase 1 studies focus primarily on safety, but will also evaluate the vaccines' potential to reduce the amount of virus in the mother and to stimulate antibodies that will prevent infection of the fetus.

In August 1994, FDA approved the antiviral Retrovir (zidovudine, or AZT) to help prevent maternal-fetal transmission of HIV. A study of the drug for this use was halted early when preliminary data showed extremely encouraging results: that 8.3 percent of babies born to HIV-infected pregnant women treated with the drug became infected, compared with 25.5 percent of babies born to women on placebo. (See "Mother and Child—The HIV Connection," page 29.)

Breast Cancer Trials

FDA has also been involved in a project to determine what resources are available for women seeking information about clinical trials of breast cancer treatments.

A 1995 study by FDA's Office of Special Health Issues and the agency's Office of Women's Health determined that there was no central source of clinical trials information that included both federally and privately sponsored clinical trials of breast cancer therapies.

The FDA researchers found that, in most cases, women seeking information about investigational drug studies directly from most university centers or other clinics were referred back to their doctors. Generally, only the Cancer Information Service (1-800-422-6237) of the National Cancer Institute provided information on trials being conducted both at NCI and elsewhere. However, NCI, which relies mostly on its Physician Data Query (PDQ) database, did not usually have information about privately funded cancer research.

As a result, after consulting with NCI officials, FDA asked the Pharmaceutical Research and Manufacturers Association to encourage its members to submit information about their non-federally-funded clinical trials to NCI's PDQ database. FDA and NCI also sent a letter to industry sponsors of drug trials informing them that they may submit information about active cancer clinical trials to NCI for possible inclusion in the PDQ database.

The days of routinely excluding women from clinical trials seem to be over. In fact, gender difference in drug effect is a growing area of research. In 1997, studies focusing on women included those on HIV, heart disease, various cancers, weight and eating disorders, menopause, and psychiatric disorders. It is hoped that information from such studies will improve the lives of women in the years to come. ■

Judith Levine Willis is editor of this special issue. Marian Segal also contributed to this article.

Losing Weight Safely

by Marilynn Larkin

Americans trying to lose weight have plenty of company. According to a Gallup poll, about 24 percent of women are seriously trying to lose weight at any given time (as compared with 11 percent of men).

And according to a report from the Institute of Medicine (IOM), tens of millions of Americans spend more than $33 billion yearly on weight-reduction products, such as diet foods and drinks.

Yet, studies over the last two decades by the National Center for Health Statistics show that obesity in the United States is actually on the rise. Today, approximately 35 percent of women and 31 percent of men age 20 and older are considered obese, up from approximately 30 percent and 25 percent, respectively, in 1980.

The words obesity and overweight are generally used interchangeably. However, according to the IOM report, their technical meanings are not identical. Overweight refers to an excess of body weight that includes all tissues, such as fat, bone and muscle. Obesity refers specifically to an excess of body fat. It is possible to be overweight without being obese, as in the case of a body builder who has a substantial amount of muscle mass. It is possible to

The first step in losing weight safely is to determine a realistic weight goal.

be obese without being overweight, as in the case of a very sedentary person who is within the desirable weight range but who nevertheless has an excess of body fat. However, most overweight people are also obese and vice versa. Men with more than 25 percent and women with more than 30 percent body fat are considered obese.

Many people who diet fail to lose weight—or, if they do lose, fail to maintain the lower weight over the long term. As the IOM report, "Weighing The Options: Criteria for Evaluating Weight-Management Programs," points out, obesity is "a complex, multifactorial disease of appetite regulation and energy metabolism."

Because many factors affect how much or how little food a person eats and how that food is metabolized, or processed, by the body, losing weight is not simple. For example, recent studies suggest a role for genetic makeup in obesity. This area is still controversial, and more studies will be needed before scientists can say with certainty that a person's genes may set limits on how much weight can be lost and maintained.

Yet many people persist in seeking simple cures to this complex health problem. Lured by fad diets or pills that promise a quick and easy path to thinness, they end up disappointed when they regain lost weight.

"When it comes to weight loss, if something sounds too good—or too easy, or too delicious—to be true, it probably is," says Victor Herbert, M.D., J.D., professor of medicine and director of the Nutrition Center at the Mount Sinai School of Medicine and Bronx VA Medical Centers in New York City, and member of the board of directors of the National Council Against Health Fraud. "If a weight loss claim is sensational, it is not true; if it is true, it is not sensational."

Obesity a Disease

Obesity is now considered a disease—not a moral failing. According to a new report from the Institute of Medicine, "obesity is a heterogeneous disease in which genetic, environmental, psychological, and other factors are involved. It occurs when energy intake exceeds the amount of energy expended over time. Only in a small minority of cases is obesity caused by such illnesses as hypothyroidism or the result of taking medications, such as steroids, that can cause weight gain."

Public health concerns about this disease relate to its link to numerous other diseases that can lead to premature illness or death. The report notes that overweight individuals who lose even relatively small amounts of weight are likely to:

- lower their blood pressure (and thereby the risk of heart attack and stroke)
- reduce abnormally high levels of blood glucose (associated with diabetes)
- bring blood levels of cholesterol and triglycerides (associated with cardiovascular disease) down to more desirable levels
- reduce sleep apnea, or irregular breathing during sleep
- decrease the risk of osteoarthritis of the weight-bearing joints
- decrease depression
- increase self-esteem.

Of course, losing excess weight is also likely to improve appearance, which is a strong motivation for many people.

To order a copy of the IOM report, call (1-800) 624-6242 (in Washington, D.C., call 202-334-3313). The cost is $30 plus $4 shipping and handling. ■

—M.L.

To help consumers plan a healthful diet, FDA and USDA have revamped food labels.

No Shortcuts

"There are no shortcuts—no magic pills," adds Lori Love of the Food and Drug Administration's Center for Food Safety and Applied Nutrition. Losing weight sensibly and safely requires a multifaceted approach that includes setting reasonable weight-loss goals, changing eating habits, and getting adequate exercise. Appetite suppressants (diet pills) or other products may help some people over the short term, but they are not a substitute for adopting healthful eating habits over the long term.

The first step in losing weight safely is to determine a realistic weight goal. Two types of tables are commonly used as guidelines. One is the weight-for-height table developed in 1990 by the U.S. Department of Agriculture and the Department of Health and Human Services. This table offers a range of suggested weights for adults based on height and age.

Another table uses body mass index (BMI), a mathematical formula that correlates weight with body fat. In 1993, the National Institute of Diabetes and Digestive and Kidney Diseases developed a table that correlates height, weight and BMI.

A physician or other health provider can help you set a reasonable goal with these tables. To reach the goal safely, plan to lose 1 to 2 pounds weekly by consuming approximately 300 to 500 fewer calories daily than usual. Women and inactive men generally need to consume approximately 2,000 calories to maintain weight; men and very active women may consume up to 2,500 calories daily without gaining weight.

Moderation, Variety and Balance

After determining a reasonable goal weight, devise an eating plan based on the cornerstones of healthful eating—moderation, variety and balance, suggests Herbert.

"Moderation means not eating too much or too little of any particular food or nutrient. Variety means eating as wide a variety as possible from each, and within each, of the five basic food groups. Balance refers to the balance achieved by following moderation and variety, as well as the balance of calories consumed versus calories expended," he explains. To lose weight, fewer calories should be consumed than expended; to maintain weight loss, the number of calories consumed and expended should be about the same.

The five basic food groups and the recommended number of servings from each are incorporated into the Food Guide Pyramid developed by USDA and HHS. These groups are (1) bread, cereal, pasta, and rice; (2) vegetables; (3) fruits; (4) milk, yogurt and cheese; and (5) meat, poultry, fish, dry beans, eggs, and nuts. A sixth group (fats, oils and sweets) consists mainly of items that are pleasing to the palate but high in fat and/or calories; these should be eaten in moderation.

Using the Food Label

To help consumers plan a healthful diet, FDA and USDA have revamped food labels. By law, most food labels now must display a Nutrition Facts panel containing information about how the food can fit into an overall daily diet. Nutrition Facts state how much saturated fat, cholesterol, fiber, and certain nutrients are contained in each serving. Serving sizes must now be based on standards set for similar kinds of food, so the nutritional value of similar products may be compared.

On the food label, "%Daily Value" shows what percentage of a given nutrient is provided in one portion for daily diets of 2,000 and 2,500 calories.

Whether or not a given food fits into a weight-loss diet depends on what other foods you eat that day. For most people, the goal is to select a variety of foods that together add up to approximately 100 percent of the Daily Value for total carbohydrate, dietary fiber, vitamins, and minerals; total fat, cholesterol and sodium each may add up to less than 100 percent.

This system permits a good deal of flexibility. No food is inherently "bad"; it is the total diet for the day that counts. You may compensate for an occasional rich dessert or serving of fried food by eating foods that are low in fat, oil or sugar for the rest of the day. However, high-fat foods should be limited, because they can quickly use up a day's supply of calories without providing high percentages of vital nutrients.

Simple modifications in food selection and preparation allow you to include traditional favorites and snacks within the context of a healthful weight-loss diet: for example, select 1 percent or skim milk products instead of those made with whole milk, lean cuts of meat and poultry, and nonfat frozen yogurt instead of ice cream. Low-fat plain yogurt may be substituted for sour cream in dips, dressings or spreads, and reduced-fat cheeses may be used instead of those made from whole milk. Broil, roast or steam foods instead of frying.

Look on the nutrition label for words such as "low," "light" or "reduced" to describe the calorie and fat content per serving. These foods must have significantly fewer calories or significantly less fat than similar products that do not make these claims. Foods that are advertised as "low in cholesterol" also must be low in saturated fat.

Foods that claim to contain fewer calories or less fat than similar servings of similar products must show the difference on the label. For example, on a container of low-fat cottage cheese, the label would show that a serving of the low-fat product contains 80 calories and 1.5 grams of fat while regular cottage cheese contains 120 calories and 5 grams of fat per serving.

Include small portions of desserts or

Regular exercise is important for overall health as well as for losing and maintaining weight.

high-fat snacks rather than attempting to cut them out altogether. Eliminating favorite foods may result in cravings that can lead to binge eating and weight gain.

Avoid low-calorie fad diets that exclude whole categories of food such as carbohydrates (bread and pasta) or proteins (meat and poultry). These diets may be harmful because they generally do not include all nutrients necessary for good health. "Every fad diet that demands an unusual eating pattern, such as emphasizing only a few types of foods, deviates from one or more of the guidelines of moderation, variety and balance," says Herbert. "The greater the deviation, the more harmful the diet is likely to be."

Exercise

Regular exercise is important for overall health as well as for losing and maintaining weight. There is evidence to suggest that body fat distribution affects health risks. For example, excess fat in the abdominal area (as opposed to hips and thighs) is associated with greater risk for high blood pressure, diabetes, early heart disease, and certain types of cancer.

This "apple shape" is more common in men than in women, who more often gain weight in the hips and thighs, in what is sometimes referred to as a "pear shape." Exercise is recommended no matter what your shape since it can prevent or reduce fat anywhere on the body, but from a health standpoint it is more urgent for those with "apple" shapes in order to lower disease risks.

A half hour of brisk walking or other aerobic activity three times weekly can help the body use up calories consumed daily as well as excess calories stored as fat. Weight-bearing exercises also help tone muscles and may reduce the risk of osteoporosis.

Diet Pills

The 1991/1992 Weight Loss Practices Survey, sponsored by FDA and the National Heart, Lung, and Blood Institute, found that 5 percent of women and 2 percent of men trying to lose weight use diet pills. Products considered by FDA

to be over-the-counter weight control drugs are primarily those containing the active ingredient phenylpropanolamine (PPA), such as Dexatrim and Acutrim. PPA is available over the counter (OTC) for weight control in a 75-mg controlled-release dosage form, when combined with a restricted diet and exercise.

Using diet pills containing PPA will not make a big difference in the rate of weight loss, says Robert Sherman of FDA's Office of OTC Drug Evaluation. "Even the best studies show only about a half pound greater weight loss per week using PPA combined with diet and exercise," he adds. Sherman cautions that the recommended dosage of these pills should not be exceeded because of the risk of adverse effects, such as elevated blood pressure and heart palpitations.

Since PPA is also used as a nasal decongestant in over-the-counter cough and cold products, consumers should read the labels of OTC decongestants to see if they contain PPA. They should not take PPA in two products labeled for different uses.

Sherman notes that FDA has received a small number of reports indicating that PPA use might be associated with an increased risk of stroke. A large-scale safety study was begun in September 1994 to explore the possibility. Based on available data, the agency does not believe that an increased risk of stroke is a concern when PPA is used at recommended dosages.

For many years, amphetamines were the primary prescription medications to treat obesity. Amphetamines act as stimulants and can be addictive. They are approved for short-term use only, in conjunction with reduced-calorie diets.

In April 1996, FDA approved Redux (dexfenfluramine) for more prolonged treatment of obesity than drugs previously approved, in conjunction with reduced-calorie diets. Redux belongs to a class of drugs called serotonin uptake inhibitors. They suppress appetite by releasing serotonin—a brain chemical associated with reduction of appetite—and slowing its depletion. Some antidepressants that affect serotonin similarly include Prozac (fluoxetine), Zoloft (sertraline), and Paxil (paroxetine). People shouldn't take both antidepressants and appetite suppressants without consulting their physicians. Taking more than one serotonin uptake inhibitor at once could result in an overdose, causing tremors, seizures, and possibly organ failure.

A rare but serious—and possibly life-threatening—side effect, a lung disorder called pulmonary hypertension, has been reported to have an incidence in those taking Redux and a chemically related appetite suppressant, Pondimin (fenfluramine), of 24 to 46 per million patients per year. Symptoms of pulmonary hypertension include breathing difficulty, chest pain, faintness, and swelling in lower legs or ankles. People taking appetite suppressants should immediately seek medical help if these symptoms develop.

In letters sent to more than 300,000 health-care providers, including about 155,000 physicians, the manufacturer and distributor of Redux advised that the findings on the higher risk of pulmonary hypertension reinforce the conclusion that Redux should not be used for "cosmetic" weight loss.

Redux is approved for obese patients whose initial BMI is at least 30 (for example, someone who is 5 feet 6 inches and weighs 185 pounds or more). Patients with other risk factors, such as high blood pressure or diabetes, can be treated with the drug if their BMI is 27 or higher (for example, someone who is 5 feet 6 inches and weighs 167 pounds or more). Long-range safety and effectiveness data are not available for use of Redux for more than one year.

A revised patient package insert discusses the potential risk of pulmonary hypertension so that patients can make an informed choice about taking the drug. The company has also agreed, under an enhanced program to monitor adverse reactions, to report cases of pulmonary hypertension to FDA within 15 days.

The combination of two drugs, fenfluramine (marketed as Pondimin) and phentermine (marketed as Adipex, Fastin, and others), was reported in July 1997 to be associated with heart valve problems. FDA approved the drugs separately more than 20 years ago for short-term treatment of obesity. However, in the mid-'90s some doctors were prescribing the two drugs in combination (known as fen-phen) for long-term management of obesity. FDA is unaware of studies adequately demonstrating the combination's safety and effectiveness.

In a letter to doctors, FDA said that as of July 8, 1997, it had received reports of 33 cases of heart valve abnormalities in women aged 30 to 72 who had been taking the combination for 1 to 28 months. The agency also notified the drugs' manufacturers that it wanted to meet with them to discuss labeling changes.

All prescription appetite suppressant drugs should be taken only under careful medical supervision.

Weight-Loss Programs

Many people turn to weight-loss programs for help in planning a daily diet and changing lifestyle habits. The IOM report provides guidelines for evaluating the potential effectiveness of such programs.

"To improve their chances for success, consumers should choose programs that focus on long-term weight management; provide instruction in healthful eating, increasing activity, and improving self-esteem; and explain thoroughly the potential health risks from weight loss," according to the report. Consumers should also demand evidence of success. If it is absent or consists primarily of testimonials or other anecdotal evidence, "the program should be viewed with suspicion."

IOM recommends that potential clients be given a truthful, unambiguous, nonmisleading statement about the program's approaches and goals, and a full disclosure of costs. The cost breakdown should include initial and ongoing costs, as well as the cost of extra products.

The basic tenet of weight loss—to eat fewer calories than you burn and to stay active—is easy to say but, like most lifestyle changes, not so easy to do. With realistic goals, and a commitment to losing weight slowly, safely and sensibly, the chances of long-term success improve dramatically. ■

Marilynn Larkin is a medical writer in New York City.

Eating Disorders

Require Medical Attention

by Dixie Farley

For reasons that are unclear, some people—mainly young women—develop potentially life-threatening eating disorders called bulimia nervosa and anorexia nervosa. People with bulimia, known as bulimics, indulge in bingeing (episodes of eating large amounts of food) and purging (getting rid of the food by vomiting or using laxatives). People with anorexia, whom doctors sometimes call anorectics, severely limit their food intake. About half of them also have bulimia symptoms.

The National Center for Health Statistics estimates that about 9,000 people admitted to hospitals were diagnosed with bulimia in 1994, the latest year for which statistics are available, and about 8,000 were diagnosed with anorexia. Studies indicate that by their first year of college, 4.5 to 18 percent of women and 0.4 percent of

Disorders' Definitions

According to the American Psychiatric Association, a person diagnosed as bulimic or anorectic must have all of that disorder's specific symptoms:

Bulimia Nervosa

- recurrent episodes of binge eating (minimum average of two binge-eating episodes a week for at least three months)
- a feeling of lack of control over eating during the binges
- regular use of one or more of the following to prevent weight gain: self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise
- persistent over-concern with body shape and weight.

Anorexia Nervosa

- refusal to maintain weight that's over the lowest weight considered normal for age and height
- intense fear of gaining weight or becoming fat, even though underweight
- distorted body image
- in women, three consecutive missed menstrual periods without pregnancy. ■

men have a history of bulimia and that as many as 1 in 100 females between the ages of 12 and 18 have anorexia.

Males account for only 5 to 10 percent of bulimia and anorexia cases. While people of all races develop the disorders, the vast majority of those diagnosed are white.

Most people find it difficult to stop their bulimic or anorectic behavior without professional help. If untreated, the disorders may become chronic and lead to severe health problems, even death. Antidepressants are sometimes prescribed for people with these eating disorders, and in November 1996, FDA added the treatment of bulimia to the indications for the antidepressant Prozac (fluoxetine).

About 1,000 women die of anorexia each year, according to the American Anorexia/Bulimia Association. More specific statistics from the National Center for Health Statistics show that "anorexia" or "anorexia nervosa" was the underlying cause of death noted on 101 death certificates in 1994, and was mentioned as one of multiple causes of death on another 2,657 death certificates. In the same year, bulimia was the underlying cause of death on two death certificates and mentioned as one of several causes on 64 others.

As to the causes of bulimia and anorexia, there are many theories. One is that some young women feel abnormally pressured to be as thin as the "ideal" portrayed by magazines, movies and television. Another is that defects in key chemical messengers in the brain may contribute to the disorders' development or persistence.

The Bulimia Secret

Once people begin bingeing and purging, usually in conjunction with a diet, the cycle easily gets out of control. While cases tend to develop during the teens or early 20s, many bulimics successfully hide their symptoms, thereby delaying help until they reach their 30s or 40s. Several years ago, actress Jane Fonda revealed she had been a secret bulimic from age 12 until her recovery at 35. She told of bingeing and purging up to 20 times a day.

Many people with bulimia maintain a nearly normal weight. Though they appear healthy and successful—"perfectionists" at whatever they do—in reality, they have low self-esteem and are often depressed. They may exhibit other compulsive behaviors. For example, one physician reports that a third of his bulimia patients regularly engage in shoplifting and that a quarter of the patients have suffered from alcohol abuse or addiction at some point in their lives.

Once people begin bingeing and purging, usually in conjunction with a diet, the cycle easily gets out of control.

While normal food intake for a women and teenagers is 2,000 to 3,000 calories in a day, bulimic binges average about 3,400 calories in 1¼ hours, according to one study. Some bulimics consume up to 20,000 calories in binges lasting as long as eight hours. Some spend $50 or more a day on food and may resort to stealing food or money to support their obsession.

To lose the weight gained during a binge, bulimics begin purging by vomiting (by self-induced gagging or with an emetic, a substance that causes vomiting) or by using laxatives (50 to 100 tablets at a time), diuretics (drugs that increase urination), or enemas. Between binges, they may fast or exercise excessively.

Extreme purging rapidly upsets the body's balance of sodium, potassium, and other chemicals. This can cause fatigue, seizures, irregular heartbeat, and thinner bones. Repeated vomiting can damage the stomach and esophagus (the tube that carries food to the stomach), make the gums recede, and erode tooth

Obsessed with weight loss and fear of becoming fat, anorectics see normal folds of flesh as "fat" that must be eliminated.

enamel. (Some patients need all their teeth pulled prematurely.) Other effects include various skin rashes, broken blood vessels in the face, and irregular menstrual cycles.

Complexities of Anorexia

While anorexia most commonly begins in the teens, it can start at any age and has been reported from age 5 to 60. Incidence among 8- to 11-year-olds is said to be increasing.

Anorexia may be a single, limited episode with large weight loss within a few months followed by recovery. Or it may develop gradually and persist for years. The illness may go back and forth between getting better and getting worse. Or it may steadily get more severe.

Anorectics may exercise excessively. Their preoccupation with food usually prompts habits such as moving food about on the plate and cutting it into tiny pieces to prolong eating, and not eating with the family.

Obsessed with weight loss and fear of becoming fat, anorectics see normal folds of flesh as "fat" that must be eliminated. When the normal fat padding is lost, sitting or lying down brings discomfort, not rest, making sleep difficult. As the disorder continues, victims may become isolated and withdraw from friends and family.

The body responds to starvation by slowing or stopping certain bodily processes. Blood pressure falls, breathing rate slows, menstruation ceases (or, in girls in their early teens, never begins), and activity of the thyroid gland (which regulates growth) diminishes. Skin becomes dry, and hair and nails become brittle. Lightheadedness, cold intolerance, constipation, and joint swelling are other symptoms. Reduced fat causes the body temperature to fall. Soft hair called lanugo forms on the skin for warmth. Body chemicals may get so imbalanced that heart failure occurs.

Anorectics who additionally binge and purge impair their health even further. The late recording artist Karen Carpenter, an anorectic who used syrup of ipecac to induce vomiting, died after buildup of the drug irreversibly damaged her heart.

Getting Help

Early treatment is vital. As either disorder becomes more entrenched, its damage becomes less reversible.

Usually, the family is asked to help in the treatment, which may include psychotherapy, nutrition counseling, behavior modification, and self-help groups. Therapy often lasts a year or more—on an outpatient basis unless life-threatening physical symptoms or severe psychological problems require hospitalization. If there is deterioration or no response to therapy, the patient (or parent or other advocate) may want to talk to the health professional about the plan of treatment.

There are no drugs approved specifically for bulimia or anorexia, but several, including some antidepressants, are being investigated for this use.

If you think a friend or family member has bulimia or anorexia, point out in a caring, nonjudgmental way the behavior you have observed and encourage the person to get medical help. If you think you have bulimia or anorexia, remember that you are not alone and that this is a health problem that requires professional help. As a first step, talk to your parents, family doctor, religious counselor, or school counselor or nurse. ■

Dixie Farley is a staff writer for FDA Consumer.

For More Information

If you want more information about bulimia and anorexia, send your request and a stamped, self-addressed, business-size envelope to:

American Anorexia/Bulimia Association, Inc.
239 Central Park West
Suite 1R
New York, NY 10024
(212) 501-8351
http://members.aol.com/amanbu/index.html

National Association of Anorexia Nervosa and Associated Disorders
P.O. Box 7
Highland Park, IL 60035
(847) 831-3438

TSS

Reducing the Risk

by Dixie Farley

Women taking the necessary measures to prevent menstrually-related toxic shock syndrome (TSS) can be credited with much of the reduction in the number of cases in recent years. In 1995, the latest year for which figures were available when this special issue went to press, there had been only nine confirmed menstrually-related TSS cases and no deaths.

TSS is a rare but potentially fatal disease that, when related to menstruation, occurs most frequently in young women aged 15 to 24, usually in association with tampon use.

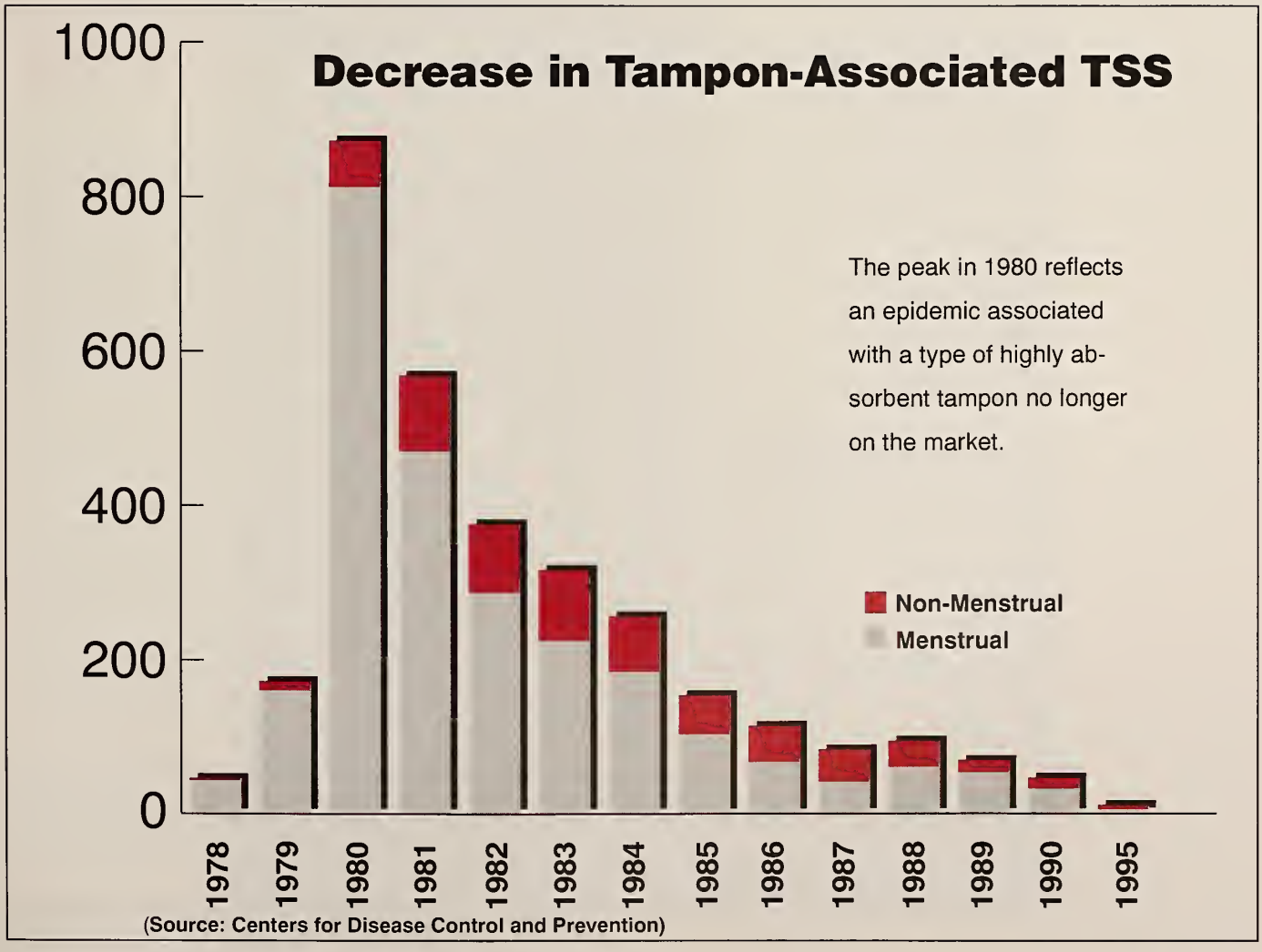
The number of confirmed menstrually-related TSS cases peaked in 1980 at 814, with 38 deaths. The national Centers for Disease Control found that 71 percent of women who developed the condition had been using Rely, a brand of highly absorbent tampon that had recently come on the market. These tampons were removed from the market, and the Food and Drug Administration and tampon manufacturers developed product labeling to help women avoid the life-threatening condition.

The incidence of menstrually-related TSS was reduced to 470, with 13 deaths, in 1981 and has continued to fall steadily since then.

TSS was first identified as a distinct disease in 1978 and also affects people who don't use tampons. It occurs in children, men, and non-menstruating women, most frequently in connection with wounds. Though scientists know there is a relationship between the development of TSS and the use of tampons, especially high-absorbency tampons, the exact connection remains unclear.

Scientists think that in order for the disease to develop, bacteria called *Staphylococcus*

If you get flu-like symptoms during or just after your menstrual period, it's a good idea to check with your doctor. You may have TSS.



aureus must be present. These bacteria release one or more toxins (poisons) into the bloodstream. *S. aureus* bacteria commonly live in body areas such as the nose, skin or vagina and usually cause no problem. "But the bacteria also can lead to serious infection after a deep wound or surgery or, for reasons not fully understood, during tampon use."

Keeping Your Risk Low

If you've ever had TSS, get medical advice before using tampons.

You can reduce your risk of TSS by not using tampons, or by alternating between tampons and pads. Whether the benefits of using tampons—particularly high-absorbency ones—are worth the increased risk of TSS is an individual decision.

Because the TSS risk increases with tampon absorbency, if you use tampons, you should use products with the lowest absorbency that meets your needs. There's usually less need for high absorbency at the end of a menstrual period. You can find what's best for you by experimenting with different sizes and different brands, beginning with the least absorbent.

To help women compare absorbency from brand to brand, FDA requires that manufacturers use a standard test to measure absorbency and that the absorbency be stated on the label using standard terminology. When shopping for tampons, look on the packages for the following absorbency terms and ranges and then compare brands before you make your selection.

If the package says:	*The absorbency range is:*
Junior Absorbency	6 grams and under
Regular Absorbency	6 to 9 grams
Super Absorbency	9 to 12 grams
Super Plus Absorbency	12 to 15 grams

It also helps to:

- Follow the manufacturer's instructions.
- Store tampons in a clean, dry place.
- Wash hands with soap and water before and after inserting or removing a tampon.
- Try a less absorbent variety if a tampon is irritating or difficult to remove.

FDA also requires manufacturers to give information about TSS on the tampon box or in a package insert. This information must include a warning about the association between TSS and high-absorbency tampons. You can stay up-to-date on TSS by reading the package information when you buy tampons and asking about TSS when you get a medical checkup.

Symptoms may not appear until the first few days after the end of your period. Be sure to explain to your doctor what your symptoms are, when your period began, and whether you've ever had TSS before. If you use tampons, mention what absorbency you use.

TSS Symptoms

Remove your tampon if you're using one and get medical help right away if you have the following symptoms during menstruation:

- sudden high fever—102 degrees Fahrenheit (or 38.9 degrees Celsius) or higher
- vomiting
- diarrhea
- muscle aches
- dizziness, fainting, or near fainting when standing up
- a rash that looks like a sunburn.

Early diagnosis and speedy treatment are crucial to avoiding the most serious effects of TSS. ■

TSS symptoms appear quickly and are often severe. Not all cases are exactly alike, and you may not have all the symptoms. You may have aching muscles, bloodshot eyes, or a sore throat, making it seem like the flu. The sunburn-like rash may not develop until you're very ill; it may go unnoticed if it's only on a small area. Later, the skin on your palms and soles may flake or peel. A first episode may be so mild that you don't connect the symptoms with TSS, but the next time, the symptoms may be severe. Once you've had TSS, you're more likely to get it than someone who never has had it.

Deaths, though rare, tend to happen during the first week of illness. The danger lies in a sudden drop in blood pressure, which could lead to shock if not treated in time.

TSS is usually treated with antibiotics and drugs to lower temperature, and large amounts of fluids and electrolytes (essential body chemicals) to raise lowered blood pressure. Blood and other specimens from the body are analyzed in a laboratory to identify bacteria. Antibiotics are also given to help prevent recurrence. Patients often are hospitalized, and severe cases require intensive care. With proper treatment, patients generally recover within three weeks.

While TSS is rare, it's an important health concern for menstruating women, and especially young women. Knowing how to prevent it and recognizing its symptoms can do much to reduce its dangers and continue to keep its incidence low. ■

Dixie Farley is a staff writer for FDA Consumer. *Judith Levine Willis also contributed to this article.*

Getting Rid Of

Yeast Infections

by Judith Levine Willis

It's an itchy feeling you might hardly notice at first.

Maybe, you muse, it's just that your jeans are too tight.

Actually, tight jeans may have something to do with it. But if the itch keeps getting itchier, even when your jeans have been off for awhile, then there's something else involved.

That something else could very well be a fungus whose technical name is *Candida*, and which causes what is often called a "yeast" infection. Such infections are most common in women aged 16 to 35, although they can occur in girls as young as 10 or 11 and in older women (and, less often, in men and boys as well). You do not have to be sexually active to get a yeast infection.

The Food and Drug Administration now allows medicines that used to be prescription-only to be sold without a prescription to treat vaginal yeast infections that keep coming back. But before you run out and buy one, if you've never been treated for a yeast infection you should see a doctor. Your doctor may advise you to use one of the over-the-counter products or may prescribe a drug called Diflucan (fluconazole). FDA recently approved the drug, a tablet taken by mouth, for clearing up yeast infections with just one dose.

Though itchiness is a main symptom of yeast infections, if you've never had one before, it's hard to be sure just what's causing your discomfort. After a doctor makes a diagnosis of vaginal yeast infection, if you should have one again, you can more easily recognize the symptoms that make it different from similar problems. If you have any doubts, though, you should contact your doctor.

In addition to intense itching, another symptom of a vaginal yeast infection is a white curdy or thick discharge that is mostly odorless. Although some women have discharges midway between their menstrual periods, these are usually not yeast infections, especially if there's no itching.

Other symptoms of a vaginal yeast infection include:

- soreness
- rash on outer lips of the vagina
- burning, especially during urination.

Though itchiness is a main symptom of yeast infections, if you've never had one before, it's hard to be sure just what's causing your discomfort.

It's important to remember that not all girls and women experience all these symptoms, and if intense itching is not present it's probably something else.

Candida is a fungus often present in the human body. It only causes problems when there's too much of it. Then infections can occur not only in the vagina but in other parts of the body as well—and in both sexes. Though there are four different types of *Candida* that can cause these infections, nearly 80 percent are caused by a variety called *Candida albicans.*

Many Causes

The biggest cause of *Candida* infections is lowered immunity. This can happen when you get run down from doing too much and not getting enough rest. Or it can happen as a result of illness.

Though not usual, repeated yeast infections, especially if they don't clear up with proper treatment, may sometimes be the first sign that a woman is infected with HIV, the virus that causes AIDS.

FDA requires that over-the-counter (OTC) products to treat yeast infections carry the following warning:

"If you experience vaginal yeast infections frequently (they recur within a two-month period) or if you have vaginal yeast infections that do not clear up easily with proper treatment, you should see your doctor promptly to determine the cause and receive proper medical care."

Repeated yeast infections can also be caused by other, less serious, illnesses or physical and mental stress. Other causes include:

- use of antibiotics and some other medications, including birth control pills
- significant change in the diet
- poor nutrition
- diabetes
- pregnancy.

Some women get mild yeast infections towards the end of their menstrual periods, possibly in response to the body's hormonal changes. These mild infections sometimes go away without treatment as the menstrual cycle progresses. Pregnant women are also more prone to develop yeast infections.

Sometimes hot, humid weather can make it easier for yeast infections to develop. And wearing layers of clothing in the winter that make you too warm indoors can also increase the likelihood of infection.

"*Candida* infections are not usually thought of as sexually transmitted diseases," says Renata Albrecht, M.D., of FDA's division of anti-infective drug products. But, she adds, they can be transmitted during sex.

Using a condom will help prevent transmission of yeast infections, just as it helps prevent transmission of more commonly sexually transmitted diseases, including HIV infection, and helps prevent pregnancy. To prevent STDs, always use a latex condom during sex, even if you are also using another form of birth control.

If one partner has a yeast infection, the other partner should also be treated

When you visit the doctor the first time you have a yeast infection, you can ask which product may be best for you and discuss the advantages of the different forms the products come in.

for it. A man is less likely than a woman to be aware of having a yeast infection because he may not have any symptoms. When symptoms do occur, they may include a moist, white, scaling rash on the penis, and itchiness or redness under the foreskin. As with females, lowered immunity, rather than sexual transmission, is the most frequent cause of genital yeast infections in males.

OTC Products

At press time, the OTC products for vaginal yeast infections have one of four active ingredients: butoconazole nitrate (Femstat 3), clotrimazole (Gyne-Lotrimin and others), miconazole (Monistat 7 and others), and tioconazole (Vagistat-1). These drugs are in the same anti-fungal family and work in similar ways to break down the cell wall of the *Candida* organism until it dissolves. FDA approved the switch of Femstat 3 from prescription to OTC status December 1996 and a similar switch for Vagistat-1 in February 1997. The others have been available OTC for a few years.

When you visit the doctor the first time you have a yeast infection, you can ask which product may be best for you and discuss the advantages of the different forms the products come in: vaginal suppositories (inserts) and creams with special applicators. Remember to read the warnings on the product's labeling carefully and follow the directions.

Symptoms usually improve within a few days, but it's important to continue using the medication for the number of days directed, even if you no longer have symptoms.

Contact your doctor if you have the following:

- abdominal pain, fever, or a foul-smelling discharge
- no improvement within three days
- symptoms that recur within two months.

OTC products are only for vaginal yeast infections. They should not be used by men or for yeast infections in other areas of the body, such as the mouth or under the fingernails.

Candida infections in the mouth are often called "thrush." Symptoms include creamy white patches that cover painful areas in the mouth or throat, or on the tongue. Because other infections cause similar symptoms, it's important to go to a doctor for an accurate diagnosis.

Wearing artificial fingernails increases the chance of getting yeast infections under the natural fingernails. Fungal infections start in the space between the artificial and natural nails, which become discolored. Treatment for these types of infections—as well as those that occur in other skin folds, such as underarms or between toes—require different products, most of which are available only with a doctor's prescription.

Knowing the causes and symptoms of yeast infections can help you take steps—such as giving those tight jeans a rest—to greatly reduce the chances of getting an infection (see accompanying article).

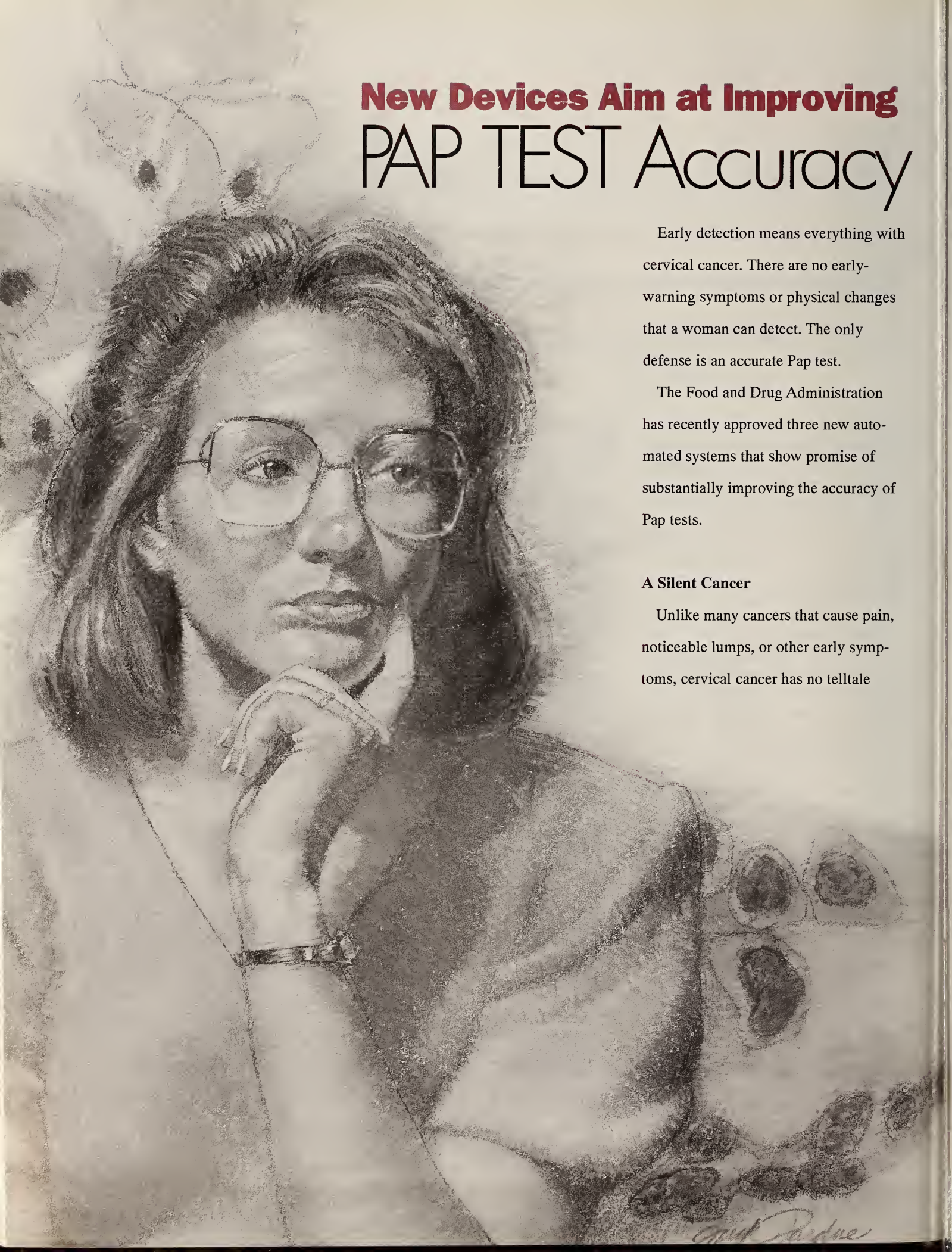
And, if sometimes prevention isn't enough, help is easily at hand from your doctor and pharmacy. ■

Judith Levine Willis is editor of this special report.

How to Avoid Infection

Here are some steps women can take to make vaginal yeast infections less likely:

- Wear loose, natural-fiber clothing and underwear with a cotton crotch.
- Limit wearing of pantyhose, tights, leggings, nylon underwear, and tight jeans.
- Don't use deodorant tampons and feminine deodorant sprays, especially if you feel an infection beginning.
- Dry off quickly and thoroughly after bathing and swimming—don't stay in a wet swimsuit for hours. ■



New Devices Aim at Improving PAP TEST Accuracy

Early detection means everything with cervical cancer. There are no early-warning symptoms or physical changes that a woman can detect. The only defense is an accurate Pap test.

The Food and Drug Administration has recently approved three new automated systems that show promise of substantially improving the accuracy of Pap tests.

A Silent Cancer

Unlike many cancers that cause pain, noticeable lumps, or other early symptoms, cervical cancer has no telltale

Finding abnormal cells is akin to finding a needle in a haystack.

symptoms until it is so advanced that it is usually unresponsive to treatment. Symptoms may even be absent at that point, although they often include abnormal vaginal bleeding, such as following intercourse or douching, between menstrual periods, or after menopause. Only in its late stages does cervical cancer cause pain in the lower abdominal or back regions.

But because the cervix, or neck of the uterus, can be easily accessed through the vagina, doctors can test for cervical cancer as well as for precancerous changes in the cervix. Most cervical cancers grow slowly over several years and often are preceded by abnormal cells. Cervical cancer can often be prevented by the removal of these abnormal cells. (See accompanying article.)

To detect abnormal or cancerous cervical cells, George Papanicolaou, M.D., Ph.D., of Cornell University developed in the 1940s what is known today as the Pap test. In this test, a sample of cells is taken from in and around the cervix with a wooden scraper, cotton swab, or small cervical brush. The specimen is smeared on a glass slide, preserved with alcohol, and then sent to a laboratory. There cytotechnologists, specially trained in identifying abnormal cells, scrutinize the cervical cells under the microscope for any abnormal features associated with cancerous or precancerous cervical cells. These features include dark or irregularly shaped cell nuclei, or small or deformed cells.

The Pap test became a routine part of gynecological exams. As a result, there was a 70 percent drop in the number of women dying from cervical cancer between 1950 and 1970, according to the National Cancer Institute. But the problem of errors remained. Such errors are understandable when considering the magnitude of the task set before the cytotechnologist examining Pap slides. These standard-sized laboratory slides are lined with between 50,000 to 300,000 cervical cells. Lurking in these cells may be as few as a dozen abnormal cells. Finding such telltale cells is akin to finding a needle in a haystack, especially at the end of the day when cytotechnologists are likely to have examined nearly 100 Pap slides. In addition, abnormalities in cell shape may be slight and difficult for even the trained eye to detect, or may be masked by infection.

Dr. George Papanicolaou. (Photo courtesy of National Library of Medicine)

Improving Detection

A new slide preparation method may improve the accuracy of the initial screening.

The ThinPrep Processor Model 2000 is an automated slide preparation system for Pap smears that may make it easier to screen for atypical cells. Safety and effectiveness data submitted by the manufacturer to FDA demonstrated that slides prepared with the ThinPrep system are significantly more effective in a variety of patient populations for detecting low-grade squamous intraepithelial lesions (SILs) and some of the more severe lesions. In addition, the ThinPrep Processor is as safe and effective as the conventional method of preparing slides by hand for detecting all categories of atypical and diseased cervical cells.

Smoking also elevates the risk of cervical cancer.

In this system, improved quality comes from an automated process that concentrates the cellular material and filters out a lot of blood and other unneeded material.

The other new systems are computerized rescreening methods. In both systems, computers scan the slides for abnormal-looking cells.

One system, called PAPNET, uses neural net computer technology, which its manufacturer claims was originally created to detect flying missiles in what is known as the "Star Wars" defense strategy. PAPNET detects abnormal cervical cells with a computer system that essentially has learned by example. This system was created by feeding a series of digitized images of Pap slides to a computer. From these examples, the computer developed the guidelines for predicting abnormal cells.

PAPNET scans each Pap slide cytotechnologists have classified as normal and chooses the 128 cells or cell clusters that are most likely to be abnormal. Enlarged color images of these cells are then returned to the cytotechnologist for review.

Studies have used PAPNET rescreening to reexamine previous negative Pap smears taken from women with high-grade cervical cell abnormalities or cervical cancers. These studies found that in about one-third of these women, PAPNET testing detected abnormalities missed by manual screening on previous Pap smears.

The other Pap test rescreening system is called AutoPap 300 QC. This computerized system uses image interproduction and pattern recognition techniques to classify cells as abnormal. Hundreds of features—such as size, shape, density, and texture—are considered for each cell. Sophisticated statistical screens use this visual information to predict which cervical cells are abnormal. Following routine screening by a cytotechnologist, all "normal" slides are rescreened by AutoPap 300 QC, which selects 10 to 20 percent of slides with the highest probability of having abnormal cells. These are then rescreened manually by the cytotechnologist.

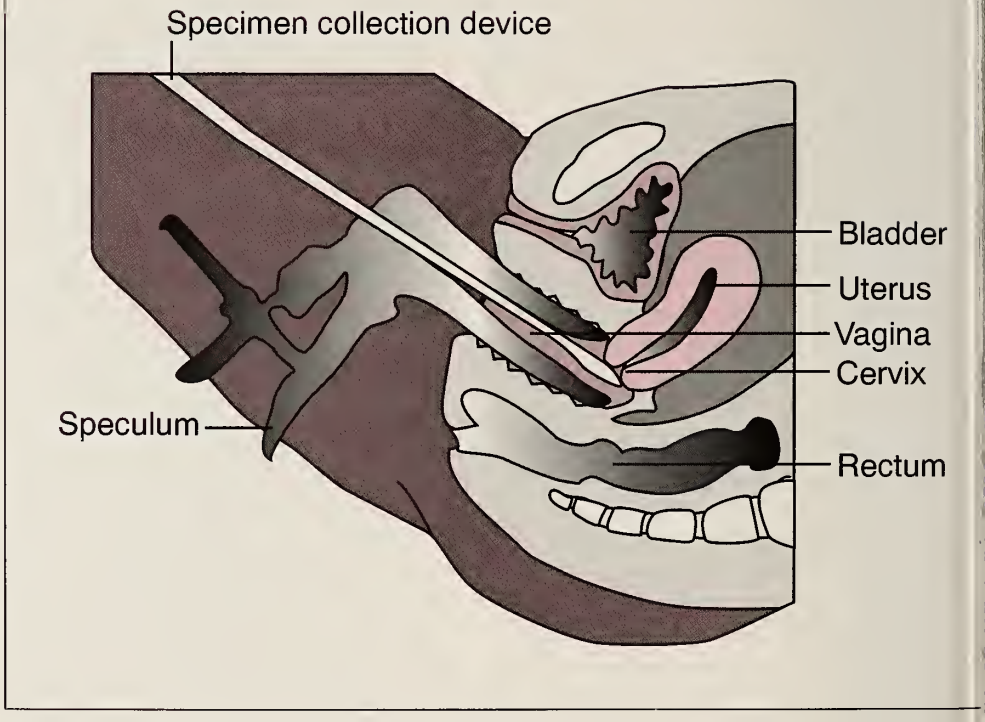
In one study, cytotechnologists randomly rescreening 10 percent of more than 4,000 Pap slides they originally classified as normal detected only about 1 of every 10 false negatives present. Cytotechnologists using AutoPap 300 QC to select the 10 percent of slides the system deemed as being most abnormal detected up to half of all the missed abnormals.

All three products are available for use by laboratories, but some labs may not yet be fully familiar with these new systems.

"Laboratories are starting to evaluate these devices and determine if and how they will use them," said Louise Magruder, of FDA's division of clinical laboratory devices.

Although use of ThinPrep, PAPNET and AutoPap 300 QC will considerably

How a Pap Test Is Done



With the woman lying on her back, the health professional inserts a speculum into the vagina. The speculum allows visualization of the cervix and the introduction of the specimen-collecting device.

Early Detection Gives Time for Treatment

Most cervical cancers gradually progress over a period of years without immediately invading nearby tissue. Yet they leave telltale signposts along their way. Even the transition from a normal to a cancerous cervical cell is usually a gradual one, with several steps that can be seen with the aid of a microscope.

In what is thought to be one of the first steps in the development of cervical cancer, the nuclei of cervical cells enlarge and darken. A patch of these abnormal cells is termed a squamous intraepithelial lesion (SIL) because the abnormal cells are present only in the squamous epithelial cells which line the surface of the cervix. SILs are further classified as low-grade if the abnormal cells are of normal size, or high-grade if the cells are smaller than normal.

Low-grade SILs are common; most spontaneously revert to normal. But because some will progress to high-grade SILs and then to cervical cancer, most doctors ask women with this Pap diagnosis to have Pap tests every four to six months for about two years. After three consecutive Pap tests come back negative, women can return to a routine screening protocol.

If repeated Pap tests show persistent abnormalities, however, a woman's doctor may want to confirm the low-grade SIL diagnosis by further scrutinizing the cervix with other procedures.

Colposcopy is a widely used method to check the cervix for abnormal areas. The doctor applies special stains to the cervix and then uses an instrument much like a microscope (called a colposcope) to detect abnormal cells, which turn a different color than healthy cells.

The doctor also may want to remove a small amount of cervical tissue for examination with a biopsy. It also may be necessary to scrape more tissue from inside the cervical opening. These procedures can be done in the doctor's office under local anesthesia.

If the low-grade SIL diagnosis is confirmed, a doctor may ask the patient to continue to have frequent Pap tests. Alternatively, the doctor may prefer to destroy the abnormal area by freezing it (cryosurgery), burning it (cauterization), or by removing it with a laser or electrosurgical device. Such treatment may cause cramping or other pain, bleeding, or a watery discharge.

High-grade SILs rarely regress spontaneously. Most progress to cervical cancer over a period of 10 to 15 years, according to the National Cancer Institute. Women who have high-grade SIL Pap reports usually are asked to undergo a colposcopy or biopsy procedure to confirm diagnosis. Once the high-grade SIL diagnosis is certain, doctors usually destroy the lesion with one of the procedures described in the previous paragraph. Or, the lesion and adjacent tissue may be surgically removed.

If a high-grade SIL progresses to the point that the cell nuclei become jagged or irregular in shape, extremely dark, and enlarged, and the cells themselves are strangely shaped (tadpole- or spindle-shaped, for example, instead of round), the lesion is considered cancerous. If the cancer is limited in scope, it may be treated with some of the same methods used to destroy precancerous lesions. For more widespread cancers, more involved surgery is usually done, removing a larger portion of the cervix or the entire uterus, ovaries or fallopian tubes. Depending on the size and location of the tumor, radiation therapy or chemotherapy may also be necessary. ■

Cervical cancer has no telltale symptoms until it is so advanced that it is usually unresponsive to treatment.

decrease the likelihood of missing a diagnosis of cervical cancer, none of these systems is perfect. Even if the rescreening systems could detect every abnormal cell on a Pap slide, some women with cervical cancer would still be told their Pap tests were normal because there were too few cells on the slide or the cell samples were not taken from both the inside and surface of the cervix. Douching or using vaginal spermicides or medicines a day or two before a Pap test can also wash away abnormal cells and thus reduce the test's accuracy.

Also, there is a small percentage of women who develop a rare form of aggressive cervical cancer that can develop to an advanced stage in less than a year. In addition, cervical cancer will continue to occur in women who don't receive regular gynecological exams and Pap tests. Most health professionals recommend that all women who are or have been sexually active or have reached age 18 have a Pap smear and gynecological exam as frequently as each year, but at least every three years, depending on their risk factors for cervical cancer.

There may be one exception to this recommendation: Researchers at Louisiana State University, writing in the Nov. 21, 1996, issue of the *New England Journal of Medicine*, found that the benefits of Pap tests for most women who have had hysterectomies are limited. The Pap test in such women is used to detect abnormal vaginal cells, and the researchers found the tests of little value for this use in women who had had hysterectomies for reasons other than cancer.

Risk Factors

Evidence collected over the past few decades suggests several risk factors for developing cervical cancer. These include having sexual intercourse before age 18, having several sexual partners, or having a sexual partner who previously had a long-term sexual relationship with a woman who had cervical cancer.

Scientists are closely scrutinizing the sexually transmitted human papillomaviruses (HPVs), some of which cause genital warts. Research strongly suggests some types of HPVs (there are more than 60 different types) can trigger the growth of abnormal cells in the cervix and are likely to play a key role in the development of cervical cancer. Women who have HPV or whose partners have HPV have an increased risk of developing cervical cancer.

However, many women infected with HPV do not develop cervical cancer, and not all women with cervical cancer harbor HPV. This suggests other factors act with HPV to cause cervical cancer. The genital herpes virus may play a role, as may the strength of a woman's immune system. Women infected with HIV, the virus that causes AIDS, are more likely to develop cervical cancer, as are female organ transplant patients who receive drugs that suppress the immune system to prevent rejection of the new organ.

Hormones may also influence the development of cervical cancer. The labeling of oral contraceptives states that some studies have found an increased incidence of cervical cancer in women taking birth control pills, but that this may be related to factors other than the pill. Women whose mothers took the estrogen-like drug diethylstilbestrol (DES) during pregnancy to prevent miscarriage are also more likely to develop cervical cancer. (DES was used to prevent miscarriages from about 1940 to 1970.)

Smoking also elevates the risk of cervical cancer, which rises with the number of cigarettes a woman smokes each day and with the number of years she has smoked. Women exposed to other people's tobacco smoke are also more likely to develop cervical cancer.

Research suggests women can reduce their risk of cervical cancer by using barrier methods of contraception, such as the diaphragm with spermicide and condoms, probably because such methods decrease the risk of being infected by a sexually transmitted disease.

At present, early detection of precancerous tissue remains the most effective way of preventing cervical cancer. When detected in its early stages nearly all cervical cancers can be cured with minor surgery or other practices.

In contrast, fewer than 20 percent of women with advanced cervical cancer survive more than five years, even with treatment, according to the National Cancer Institute. There are nearly 5,000 deaths due to cervical cancer each year in this country. Recent data from NCI reveal that the number of cases of cervical cancer in white women under the age of 50 in the United States has been increasing 3 percent each year since 1986. In contrast, incidence rates are declining in black women of all ages and in white women over age 50. According to the World Health Organization, cervical cancer is also the most common cancer among women in developing countries. New technologies available now may enhance the value of the Pap test, but for women the most important step is getting screened. ■

"The pain was so sharp I thought I'd ruptured my appendix, but the doctor said, no, it wasn't that. It was between my periods, so I didn't connect it with menstruation. I was 16.

"Over the next 10 years, I had more and more of these 'pain attacks,' and my periods gradually became heavier and more painful.

"When I was pregnant with my first child, I was virtually pain-free. But shortly after he was born, each month around ovulation, I went to bed in tears from horrible pain. And I bled so much during menstruation I didn't dare leave the house. I went back to the doctor. It was endometriosis."

—A woman from Des Moines, Iowa

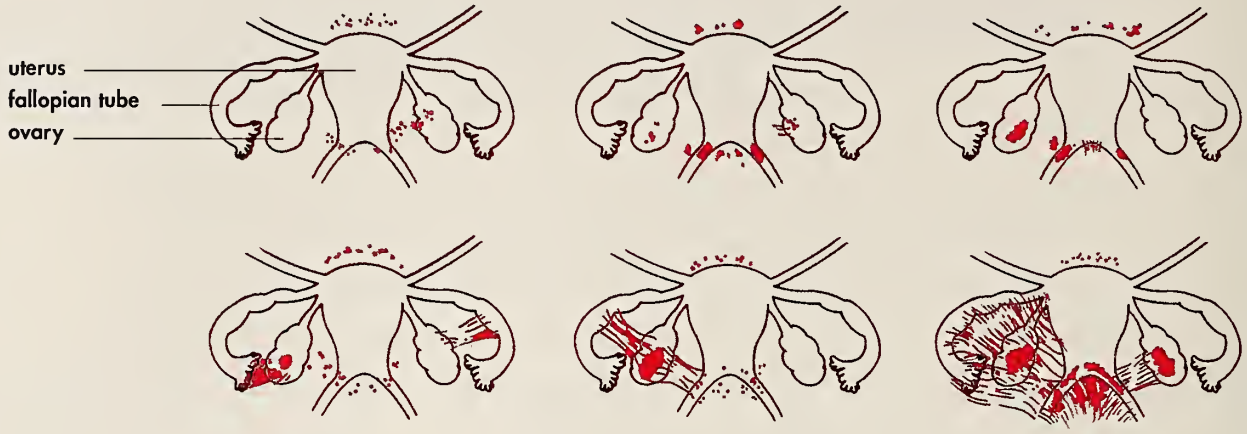
ENDOMETRIOSIS
Painful, but Treatable

by Dixie Farley

Endometriosis is a mysterious, often painful, and disabling condition in which fragments of the lining of the uterus (womb) become embedded, or implanted, elsewhere in the body.

Of the more than 3,000 patients registered with the research program of the International Endometriosis Association in Milwaukee, 41 percent report having symptoms as teenagers. About 5 million American women and girls, some as young as 11, have endometriosis, according to the association.

"These girls have terrible pain," says Lyle Breitkopf, M.D., a gynecologist in New York City. "Typically, they come to the school nurse month after month—maybe six to eight of their 12 menstrual cycles—needing something for pain or being sent home vomiting, writhing on the floor."



Endometriosis is depicted here in stages from very little disease (upper left) to severe (lower right), but not necessarily as it would progress in an individual patient.

In the upper middle sketch, endometriosis is deep in the abdomen behind the uterus. In the upper right, endometriosis affects one tube. In the lower middle, deep endometriosis attaches the left ovary to a tube and a band of tissue holding the uterus in place. In the lower right, the disease affixes both ovaries and the left tube to other tissue.
(Drawings were made from the Revised American Fertility Society Classification of Endometriosis, 1985)

For the woman from Des Moines, 25 years with endometriosis led to removal of her uterus, fallopian tubes, and ovaries a number of years ago. For many women today, new medicine and less drastic surgery reduce endometriosis symptoms and preserve reproductive organs. The Food and Drug Administration has approved several drugs to treat endometriosis and regulates medical devices, such as lasers, used in surgery.

A woman who thinks she may have endometriosis should be examined by a gynecologist. The sooner treatment begins, the better it is for the patients, says Breitkopf. "When we find them at an early stage, we can arrest the condition more easily and keep after it so it doesn't progress as far."

Doctors don't know why endometriosis only strikes certain women.

Some probably inherit it, says Breitkopf. "I've seen it in sisters, including identical twins, and in grandmother-mother-daughter situations."

According to Robert Badwey, M.D., a gynecologist in suburban Washington, D.C., "For whatever reason—greater incidence, better diagnostic techniques, or both—we're much more aware of endometriosis now than even a *few* years ago."

What's Happening in the Body?

Normally, an increased level of hormones each month triggers the release of an egg from the ovary. Finger-like tissues on one of the fallopian tubes grasp the egg, and tiny hair-like "cilia" inside the tube transport it toward the uterus. When the egg is not fertilized, the uterine lining breaks down and is shed during menstruation.

The abnormal implants of endometriosis are not in the uterus but they respond to hormonal changes controlling menstruation. Like the uterine lining, these fragments build tissue each month, then break down and bleed. Unlike blood from the lining, however, blood from implants outside the uterus has no way to leave the body. Instead, it is absorbed by surrounding tissue, which can be painful.

As the cycle recurs month after month, the implants may get bigger. They may seed new implants and form scar tissue and adhesions (scarring that connects one organ to another). Sometimes, a collection of blood called a sac or cyst forms. If a cyst ruptures, it often causes excruciating pain.

Symptoms vary from patient to patient. Severity of symptoms frequently has little to do with the extent of the implants. For instance, some women with just a few implants have severe pain, while some with many implants have little or no pain.

For some, pain starts before or during menstruation and gets worse as the period progresses. Others report pain at a variety of times during the month. There may be a sharp pain at ovulation when the egg, trying to move into the fallopian tube, causes a cyst on the ovary to burst. (Many women normally feel a twinge of pain at ovulation. Pain caused by a ruptured endometriosis cyst is severe.)

Patients whose implants affect the bladder or intestines often report painful urination or bowel movements and, sometimes, blood in the urine or stool.

Endometriosis sometimes causes premenstrual staining and, as the period progresses, heavy menstrual flow.

Often, endometriosis remains hidden a long time. A symptom such as pain at menstruation may not be seen as unusual, explains Mary Lou Ballweg, executive director of the Endometriosis Association.

"Perhaps a young woman is told by Mom, who had the same problems, that menstrual pain is normal," Ballweg says. "So she just lives with it and doesn't see a doctor until the symptoms become

Symptoms of endometriosis vary from patient to patient.

unbearable. Some young women with endometriosis have apparently normal menstrual periods for years before having discomfort and pain. Others report they've nearly always had difficult periods."

As many as 30 percent of women who report infertility problems have endometriosis.

Severe endometriosis can lead to infertility in different ways. In the ovaries, it can produce cysts that prevent the egg's release. In the fallopian tubes, implants can block the passage of the egg. Also, adhesions can fix ovaries and tubes in place so that projections on the tubes can't grasp the egg and move it into the tube. The effect of mild endometriosis on infertility is less clear.

Women with endometriosis may have a higher rate of "ectopic" pregnancy, a potentially life-threatening condition in which the fertilized egg begins to develop outside the womb.

The most common way to see whether a woman has endometriosis is by surgical examination using laparoscopy, a fairly simple procedure usually done without an overnight hospital stay. The doctor makes a tiny incision and inserts a lighted, flexible, telescope-like device called a laparoscope that allows a close look at the pelvis and internal organs. However, sometimes the implants themselves can only be seen through microscopic evaluation of biopsy specimens.

Drug Treatment

Drugs for endometriosis should not be taken by women who are, or who may be, pregnant.

The earliest drug approved to treat endometriosis was Danocrine (danazol), a synthetic steroid related to the hormone testosterone. Taken orally, in pill form, Danocrine changes endometrial tissue, shrinking and eliminating implants in some cases. Side effects include fluid retention, weight gain, and masculinizing effects such as voice change, hairiness, and reduction of breast size. Other side effects include menstrual irregularities, hot flashes, and vaginal dryness.

Other drugs, related to gonadotropin-releasing hormone (GnRH), act in a different way to decrease the hormones that make abnormal implants grow. One version is a nasal spray called Synarel (nafarelin acetate). In clinical studies, Synarel, at 400 or 800 micrograms a day (within the prescribed dosage range), was comparable to Danocrine at 800 milligrams a day (the recommended dosage) in relieving the clinical symptoms of endometriosis (such as pain) and in reducing the size of implants. Side effects include non-menstrual vaginal bleeding or ovarian cysts during the first two months of use, cessation of menstruation, hot flashes, headaches, decreased sex drive, vaginal dryness, acne, reduction in breast size, and a small loss in bone density. In clinical trials, about 10 percent of the patients experience nasal irritation from the spray.

Other drugs approved for treatment of endometriosis that are chemically related to Synarel include Lupron Depot (leuprolide acetate), a drug injected monthly into muscle, and Zoladex (goserelin acetate implant), which is injected under the skin of the upper abdomen. These drugs don't cause nasal irritation, but otherwise their side effects are similar to those of Synarel and their effectiveness is also similar.

Women taking endometriosis drugs need to watch for problems such as difficulty breathing or chest or leg pain, which may indicate a blood clot and should be reported to the doctor immediately. Other possible severe side effects include irregular heart rhythms. Frequent checkups are needed to monitor effects such as possible thinning of the bones. A patient should immediately report any new or worsened symptoms to the doctor. However, it's normal for endometriosis symptoms to *temporarily* worsen when a woman begins taking medicine.

Surgery

Sometimes medicine is not enough. Surgery may be needed to remove diseased tissue or to correct misaligned organs.

One method to remove diseased tissue combines laparoscopy with laser surgery. The laser is connected to the laparoscope and positioned so that its intense light beam is directed through the laparoscope onto the tissue to destroy it. The procedure usually is done without an overnight hospital stay and requires only about a week's recovery time at home.

"You're always reluctant to perform surgery or use medication on teenage patients," says Breitkopf. "But these young women are in terrible pain, and they can be helped. They really need to see a gynecologist so the endometriosis can be stemmed at the lowest possible stage of development."

Recurrence rates after treatment need further study, Ballweg says.

The monthly pain and heavy menstrual periods of chronic endometriosis can be frustrating, especially during the teenage years, when social and school activities are so important. Today, with diagnosis and treatment, a young woman's life can often return to normal. ■

Dixie Farley is a staff writer for FDA Consumer.

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Choosing a Treatment for UTERINE FIBROIDS

by Eleanor Mayfield

Uterine fibroids, one of the most common noncancerous gynecological conditions occurring in reproductive-age women, are estimated to affect more than 1 out of 5 women under 50 and account for 3 out of every 10 hysterectomies performed annually in the United States.

A fibroid, or myoma, is a noncancerous mass of muscle and connective tissue in the uterus (womb). No one knows what causes fibroids, but scientists believe their growth may be stimulated by the female sex hormone estrogen.

"A fibroid can be as small as a pinhead or as large as a watermelon," says Gene Williams, M.D., a medical officer in the obstetrics and gynecological devices branch of FDA's Center for Devices and Radiological Health. "It can cause no symptoms or a lot of symptoms. To the woman who has one, a fibroid may feel like a rock-hard bulge in the lower abdomen."

Every year, about 175,000 American women—most of them 35 to 55—undergo hysterectomy, or surgical removal of the uterus, as treatment for fibroids. According to American College of Obstetricians and Gynecologists guidelines, a fibroid that makes a woman's uterus bigger than it would be at 12 weeks of pregnancy, even if the woman is suffering no other symptoms, is an indication for a hysterectomy.

However, the practice of routinely recommending hysterectomy for fibroids has come under increasing scrutiny from both consumer organizations and doctors concerned about the high rate of hysterectomy in the United States. By age 60, more than a third of American women have had a hysterectomy, a rate higher than in any other Western country.

Blue Cross/Blue Shield of Illinois, in a study of all the hysterectomies performed in the state between 1987 and 1989, concluded that one-third were unnecessary. Most of the unnecessary surgeries, the insurer found, were performed for fibroids and other benign (noncancerous) conditions.

The development of endoscopes, lasers, and electrosurgical devices has led to new, less-invasive surgical techniques to remove fibroids.

Options Increase

New medications and less-invasive surgeries have made more treatment options available to women whose fibroids cause them problems. A number of doctors interviewed for this article say the most important consideration in treating a fibroid should be how the patient feels

Fibroid Types

Fibroids are classified by their position in the uterus. Intramural fibroids, the most common type, grow inside the uterine wall. Subserous or subserosal fibroids grow outward from the uterine wall into the abdominal cavity. Submucous fibroids grow inward from the uterine wall, taking up space within the uterus itself. This type of fibroid is most likely to cause symptoms of heavy, prolonged menstrual bleeding. A fibroid can be as big as 20 centimeters (nearly 8 inches) in diameter and can weigh more than 20 pounds.

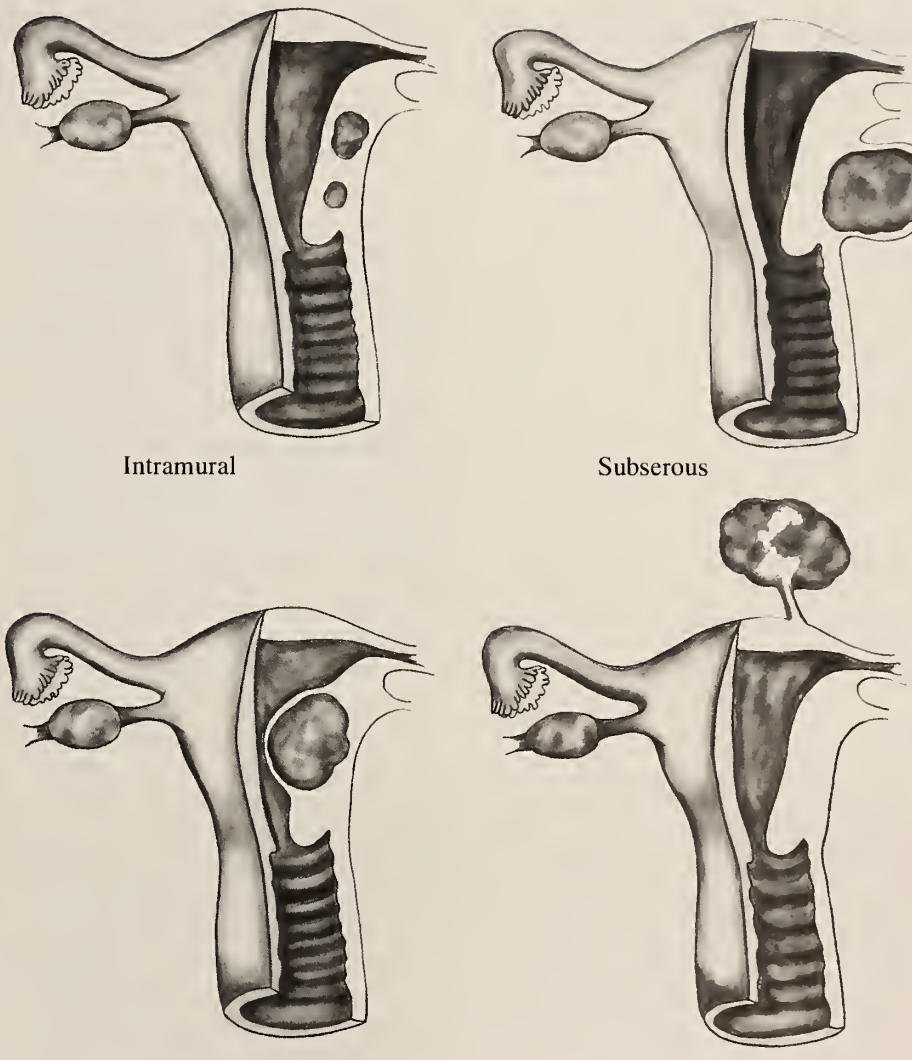
Small fibroids usually cause few if any symptoms. But, as a fibroid grows larger, it may press on the bladder and the ureters, the pair of tubes that connect the bladder to the kidneys. Pressure on the bladder can cause urinary frequency; pressure on the ureters can lead to kidney and urinary tract infections. Fibroids can sometimes be a cause of miscarriages and infertility.

A woman with a moderate-to-large fibroid may also notice a protruding stomach and a sensation of heaviness in the abdomen. For many women, the most distressing symptom is prolonged, heavy bleeding at the time of their menstrual periods, as well as spotty vaginal bleeding outside of the normal menstrual cycle. Women who lose too much blood may become anemic.

Sometimes a fibroid develops a thin stalk "like a balloon on a string," says David Barad, M.D., head of reproductive endocrinology at New York's Montefiore Medical Center. This is called a pedunculated fibroid. In some cases, the stalk can become twisted, cutting off its own blood supply, and causing severe pain.

Fibroids tend to grow in spurts, with periods of rapid growth punctuated by periods of no or very slow growth. As a woman approaches menopause, a fibroid may begin to grow rapidly. After menopause, however, fibroids stop growing and may start to shrink. ■

—E.M.



Fibroids are classified by their position in the uterus. Intramural fibroids (top left) are the most common type and grow inside the uterine wall. Subserous fibroids (top right) grow outward from the uterine wall into the abdominal cavity. Submucous fibroids (bottom left) grow inward from the uterine wall and are the most likely type to cause heavy, prolonged menstrual bleeding. Sometimes fibroids become pedunculated (bottom right), developing a thin stalk and looking like a balloon on a string. The stalk may twist, causing severe pain.

The practice of routinely recommending hysterectomy for fibroids has come under increasing scrutiny from both consumer organizations and doctors concerned about the high rate of hysterectomy in the United States.

about her condition and what level of intervention she is comfortable with.

"The physician should look objectively at the patient's symptoms, inform her of the treatment choices, and give her the autonomy to decide what she wants to do," says David Barad, M.D., director of reproductive endocrinology and infertility services at Montefiore Medical Center, Bronx, New York, and an associate professor at the Albert Einstein College of Medicine.

"There are probably hundreds of thousands of women who have fibroids on their uteruses that don't need to have anything done to them. At the other end of the spectrum, if a woman who has completed her family has a large fibroid that is causing distressing symptoms—like painful cramps, heavy menstrual bleeding, and anemia—she would be a candidate for hysterectomy."

In the March 1993 issue of the *American Journal of Obstetrics and Gynecology,* Andrew J. Friedman, M.D., and Susan T. Haas, M.D., of Harvard Medical School, write that the recommendation for surgery when fibroids make a woman's uterus larger than a 12-week pregnancy is based on three main concerns:

- Ovarian cancer might go undetected because the presence of a fibroid makes it difficult for the doctor to feel the ovaries during a pelvic examination.
- A rapidly growing fibroid may signal uterine cancer.
- A growing fibroid may produce more debilitating symptoms and add to the risks of surgery later on.

Friedman and Haas, advocating a less aggressive approach to fibroid treatment, respond to these concerns this way:

- The development of ultrasound (the use of high-frequency sound waves to produce an image of a part of the body) makes it possible to look at a woman's ovaries even when a fibroid prevents a manual examination. In any case, ovarian cancer is rare before age 50, and most hysterectomies for fibroids are done on women ages 35 to 44.
- Ultrasound and magnetic resonance imaging can be used to screen for uterine cancer, also rare in women under 50.
- Studies of hysterectomies done because of fibroids have not shown that removing a larger uterus poses a greater risk of surgical complications. "Watchful waiting" and treatment of problematic symptoms with medication or minimally invasive surgery may be just as effective as hysterectomy.

Exploring Drug Therapy

Some doctors prescribe drugs chemically similar to gonadotropin-releasing hormone (GnRH) to treat fibroids. GnRH, produced by the pituitary gland, stimulates the production of estrogen. The drugs, known as GnRH analogs, block release of the hormone, thereby preventing the production of estrogen. FDA has approved the GnRH analog Lupron Depot (leuprolide acetate) to treat preoperative anemia due to uterine fibroids. Other GnRH analogs include a nasal spray called Synarel (nafarelin acetate) and Zoladex (goserelin acetate implant). All three drugs are approved to treat endometriosis in women and prostate cancer in men. Although Synarel and Zoladex are not specifically approved for the treatment of fibroids, as with other approved medications, doctors may prescribe them if in their professional judgment a patient will benefit from them.

"Placing a woman on these drugs creates a false menopause," says Lisa Rarick, M.D., director of the division of

A number of doctors interviewed for this article say the most important consideration in treating a fibroid should be how the patient feels about her condition and what level of intervention she is comfortable with.

reproductive and urologic drug products in FDA's Center for Drug Evaluation and Research. "Her periods stop. The lack of estrogen usually causes the fibroid to shrink, just as they do after natural menopause. Sometimes other symptoms, such as pressure or pain, can be relieved by the shrinkage."

Side effects of GnRH analogs include many of the symptoms experienced by women during menopause: "hot flashes," vaginal dryness, and bone loss. Because of these side effects, the drugs are not approved for use for longer than six months. And once the medication is stopped, the fibroid usually starts to grow again.

Some gynecologists are now experimenting with combining GnRH analogs with hormone replacement therapy to "add back" lost estrogen. "This is not generally accepted clinical use as yet," says Barad. "We don't know that simply adding back estrogen will address all the safety considerations of long-term use of GnRH analogs."

Barad and others have found a useful role for GnRH analogs as preoperative therapy to shrink fibroids and stop heavy bleeding. "Both anesthesia and surgery are easier and safer if you can first make the fibroid smaller and stop the heavy bleeding so the patient isn't anemic," says Barad.

The drug Danocrine (danazol), which is chemically similar to the male sex hormone testosterone, may also be prescribed to stem heavy menstrual bleeding caused by a fibroid. Danocrine is approved for treatment of endometriosis but not for treatment of fibroids. Its main side effect is to increase male characteristics, such as facial hair and deepening of the voice; however, not all patients experience this side effect.

New Surgical Techniques

The development of endoscopes, lasers, and electrosurgical devices has led to new, less-invasive surgical techniques to remove fibroids. An endoscope is a thin fiberoptic tube that surgeons insert into the body. It can transmit an image to a television-like screen. Specialized endoscopes for viewing the abdominal cavity are called laparoscopes. Endoscopes designed to view the inside of the uterus are known as hysteroscopes. A laser is a device that uses a thin, intense light beam to "cut" or vaporize tissue, while electrosurgery or electrocautery devices use electricity to destroy tissue by applying heat.

These devices can be combined in several ways to perform a variety of procedures. Some devices combine the visualization and surgical functions in one instrument, such as the hysteroscopic rectoscope, which consists of a hysteroscope with an electrosurgery device built into it. This device is often used to remove submucous fibroids, the type most likely to cause symptoms of heavy menstrual bleeding (see "Fibroid Types").

The most appropriate procedure for each patient will depend on factors such as the size and position of the fibroid, the severity of the symptoms, and future childbearing plans. Hysterectomy, by removing the uterus, makes it impossible to become pregnant or carry a baby.

Endometrial ablation, in which an electrosurgical device is used to remove the lining of the womb, may be recommended in some situations if a woman's major fibroid-related symptom is heavy, debilitating menstrual bleeding. This procedure also makes pregnancy impossible.

Myomectomy, or surgical removal of a fibroid leaving the uterus in place, may

One Woman's Decision

In 1983, Diane Trent (not her real name), 42, began experiencing pain on the left side of her abdomen during her monthly period. Then she began to have extremely heavy periods lasting as long as two weeks. She went to see her gynecologist, who performed a pelvic examination and told her she had a fibroid in her uterus. The doctor recommended a hysterectomy.

Trent requested an ultrasound examination, which showed the fibroid was about 7 centimeters (2 3/4 inches) in diameter. She decided she only wanted to undergo a hysterectomy as a last resort and asked her doctor if there was a less drastic option.

In response, the gynecologist performed an endometrial biopsy, which showed no cancer, and a dilation and curettage (D&C), a procedure that involves dilating the cervix (the neck of the womb) and scraping the uterine lining. The D&C stemmed Trent's heavy bleeding for a while. But after a few months the problem recurred. At times, she says, the bleeding "was so disabling that I couldn't go to work." Because the fibroid was pressing on her bladder, she had to urinate frequently.

Many women in Trent's situation would have opted for a hysterectomy. Instead, Trent consulted a reproductive endocrinologist, who agreed to monitor the fibroid growth.

After three years, it had grown to 10 centimeters (4 inches) in diameter—about the size of a grapefruit. Her new doctor now recommended a hysterectomy.

"My feeling was that this was not life threatening and I didn't know what the long-term outcome of surgery would be," Trent says. "I decided I would rather put up with some discomfort that I knew would go away eventually." So she found another specialist who was willing to continue monitoring the fibroid.

The mass did not enlarge during the next five to six years. Trent is now 55. Since she reached menopause about five years ago, the fibroid has shrunk slightly. She continues to have an ultrasound examination every year. Her doctor says the fibroid should keep shrinking slowly, but it will never disappear completely.

Lisa Rarick, M.D., a medical officer in FDA's Center for Drug Evaluation and Research, says Trent's experience illustrates that the "best" treatment for a fibroid may be what the patient is most comfortable with.

"The issue is whether you can live with the symptoms. It's very individual. It depends how uncomfortable you are and how you feel about having surgery." ■

—E.M.

be an alternative to hysterectomy, particularly for women who still want to have children. In determining whether to recommend a myomectomy, a doctor will take into consideration the woman's overall health, as well as the number and location of the fibroids.

According to Barad of Montefiore, myomectomies can result in higher than average blood loss and scarring of the uterus that can adversely affect a woman's chances of becoming pregnant. "The operation you are performing to preserve reproductive potential may actually have the opposite effect."

However, newer techniques can be used to limit blood loss and preserve fertility. If the fibroid is approachable from inside the uterus, a myomectomy may be performed using a hysteroscope. This procedure may be done in a physician's office if the fibroids are small. In some cases, patients can resume normal work and leisure activities within about a week.

A woman who has discomfort and heavy menstrual bleeding caused by a large fibroid, and who does not want to become pregnant, may opt to have a hysterectomy. A traditional abdominal hysterectomy is major surgery, requiring a hospital stay and a recuperation period of about six weeks.

Women with relatively smaller fibroids may be able to have a vaginal hysterectomy instead. In this procedure, the uterus is removed through the vagina, thereby avoiding a large abdominal incision. Some doctors will prescribe GnRH analogs for several months before surgery to try to shrink the women's uterus so that a vaginal hysterectomy can be performed instead of an abdominal one. In some cases, a vaginal hysterectomy is done with the assistance of a laparoscope. Most patients will have a shorter hospital stay and recovery period for a vaginal hysterectomy than for an abdominal procedure.

Physicians differ in their approach to the treatment of fibroids, Rarick points out. "Some will only do hysterectomies. Others will do everything they can to preserve the uterus."

And Williams advises: "Patients need to ask questions and be aware of all their options." ■

Eleanor Mayfield is a writer in Silver Spring, Md.

Protecting Against *Unintended Pregnancy*

A Guide To Contraceptive Choices

by Tamar Nordenberg

I am 20 and have never gone to see a doctor about birth control. My boyfriend and I have been going together for a couple of years and have been using condoms. So far, everything is fine.

Are condoms alone safe enough, or is something else safe besides the Pill? I do not want to go on the Pill.

—Letter to the Kinsey Institute for Research in Sex, Gender, and Reproduction

Image provided by © 1994 PhotoDisc, Inc.

This young woman is not alone in her uncertainty about contraceptive options. A 1995 report by the National Academy of Sciences' Institute of Medicine, *The Best Intentions: Unintended Pregnancy and the Well-being of Children and Families,* attributed the high rate of unintended pregnancies in the United States, in part, to Americans' lack of knowledge about contraception. About 6 of every 10 pregnancies in the United States are unplanned, according to the report.

Being informed about the pros and cons of various contraceptives is important not only for preventing unintended pregnancies but also for reducing the risk of illness or death from sexually transmitted diseases (STDs), including AIDS. (See "Preventing HIV and Other STDs.")

The Food and Drug Administration has approved a number of birth control methods, ranging from over-the-counter male and female condoms and vaginal spermicides to doctor-prescribed birth control pills, diaphragms, intrauterine devices (IUDs), injected hormones, and hormonal implants. Other contraceptive options include fertility awareness and voluntary surgical sterilization.

"On the whole, the contraceptive choices that Americans have are very safe and effective," says Dennis Barbour, president of the Association of Reproductive Health Professionals, "but a method that is very good for one woman may be lousy for another."

The choice of birth control depends on factors such as a person's health, frequency of sexual activity, number of partners, and desire to have children in the future. Effectiveness rates, based on statistical estimates, are another key

About 6 of every 10 pregnancies in the United States are unplanned, according to the National Academy of Sciences.

consideration (see "Birth Control Guide"). FDA has developed a more consumer-friendly effectiveness table, which the agency will encourage all contraceptives marketers to add to their products' labeling. A copy of the table can be obtained by sending a request to FDA's Office of Women's Health (HF-8), Room 15-61, 5600 Fishers Lane, Rockville, MD 20857.

Barrier Methods

• ***Male condom.*** The male condom is a sheath placed over the erect penis before penetration, preventing pregnancy by blocking the passage of sperm.

A condom can be used only once. Some have spermicide added, usually nonoxynol-9 in the United States, to kill sperm. Spermicide has not been scientifically shown to provide additional contraceptive protection over the condom alone. Because they act as a mechanical barrier, condoms prevent direct vaginal contact with semen, infectious genital secretions, and genital lesions and discharges.

Most condoms are made from latex

rubber, while a small percentage are made from lamb intestines (sometimes called "lambskin" condoms). Condoms made from polyurethane have been marketed in the United States since 1994.

Except for abstinence, latex condoms are the most effective method for reducing the risk of infection from the viruses that cause AIDS, other HIV-related illnesses, and other STDs.

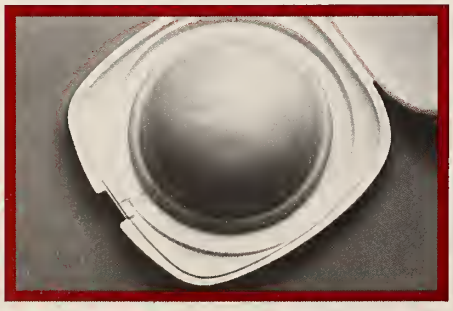
Some condoms are prelubricated. These lubricants don't provide more birth control or STD protection. Non-oil-based lubricants, such as water or K-Y jelly, can be used with latex or lambskin condoms, but oil-based lubricants, such as petroleum jelly (Vaseline), lotions, or massage or baby oil, should not be used because they can weaken the material.

• ***Female condom.*** The Reality Female Condom, approved by FDA in April

1993, consists of a lubricated polyurethane sheath shaped similarly to the male condom. The closed end, which has a flexible ring, is inserted into the vagina, while the open end remains outside, partially covering the labia.

The female condom, like the male condom, is available without a prescription and is intended for one-time use. It should not be used together with a male condom because they may not both stay in place.

• ***Diaphragm.*** Available by prescription only and sized by a health professional to achieve a proper fit, the diaphragm has a dual mechanism to prevent pregnancy. A dome-shaped rubber disk with a flexible rim covers the cervix so sperm can't reach the uterus, while a spermicide applied to the diaphragm before insertion kills sperm.



(Photos provided by Planned Parenthood Federation of America, Inc.)

The diaphragm protects for six hours. For intercourse after the six-hour period, or for repeated intercourse within this period, fresh spermicide should be placed in the vagina with the diaphragm still in place. The diaphragm should be left in place for at least six hours after the last intercourse but not for longer than a total of 24 hours because of the risk of toxic shock syndrome (TSS), a rare but potentially fatal infection. Symptoms of TSS include sudden fever, stomach upset, sunburn-like rash, and a drop in blood pressure.

• ***Cervical cap.*** The cap is a soft rubber cup with a round rim, sized by a health

professional to fit snugly around the cervix. It is available by prescription only and, like the diaphragm, is used with spermicide.

It protects for 48 hours and for multiple acts of intercourse within this time. Wearing it for more than 48 hours is not recommended because of the risk, though low, of TSS. Also, with prolonged use of two or more days, the cap may cause an unpleasant vaginal odor or discharge in some women.

• ***Sponge.*** The vaginal contraceptive sponge has not been available since the sole manufacturer, Whitehall Laboratories of Madison, N.J., voluntarily stopped selling it in 1995. It remains an approved product and could be marketed again.

Women who smoke—especially those over 35—may be advised against taking the pill.

The sponge, a donut-shaped polyurethane device containing the spermicide nonoxynol-9, is inserted into the vagina to cover the cervix. A woven polyester loop is designed to ease removal.

The sponge protects for up to 24 hours and for multiple acts of intercourse within this time. It should be left in place for at least six hours after intercourse but should be removed no more than 30 hours after insertion because of the risk, though low, of TSS.

Vaginal Spermicides Alone

Vaginal spermicides are available in foam, cream, jelly, film, suppository, or tablet forms. All types contain a sperm-killing chemical.

Studies have not produced definitive data on the efficacy of spermicides alone, but according to the authors of *Contraceptive Technology,* a leading re-

source for contraceptive information, the failure rate for typical users may be 21 percent per year.

Package instructions must be carefully followed because some spermicide products require the couple to wait 10 minutes or more after inserting the spermicide before having sex. One dose of spermicide is usually effective for one hour. For repeated intercourse, additional spermicide must be applied. And after intercourse, the spermicide has to remain in place for at least six to eight hours to ensure that all sperm are killed. The woman should not douche or rinse the vagina during this time.

Hormonal Methods

• ***Combined oral contraceptives.*** Typically called "the pill," combined oral contraceptives have been on the market for more than 35 years and are the most popular form of reversible birth control in the United States. This form of birth

control suppresses ovulation (the monthly release of an egg from the ovaries) by the combined actions of the hormones estrogen and progestin.

If a woman remembers to take the pill every day as directed, she has an extremely low chance of becoming pregnant in a year. But the pill's effectiveness may be reduced if the woman is taking some medications, such as certain antibiotics.

Besides preventing pregnancy, the pill offers additional benefits. As stated in the labeling, the pill can make periods more regular. It also has a protective effect against pelvic inflammatory disease, an infection of the fallopian tubes or uterus that is a major cause of infertility in women, and against ovarian and endometrial cancers.

The decision whether to take the pill should be made in consultation with a health professional. Birth control pills are safe for most women—safer even than delivering a baby—but they carry some risks.

Current low-dose pills have fewer risks associated with them than earlier versions. But women who smoke—especially those over 35—and women with certain medical conditions, such as a history of blood clots or breast or endometrial cancer, may be advised against taking the pill. The pill may contribute to cardiovascular disease, including high blood pressure, blood clots, and blockage of the arteries.

One of the biggest questions has been whether the pill increases the risk of breast cancer in past and current pill users. An international study published in the September 1996 journal *Contraception* concluded that women's risk of breast cancer 10 years after going off birth control pills was no higher than that of women who had never used the pill. During pill use and for the first 10 years after stopping the pill, women's risk of breast cancer was only slightly higher in pill users than non-pill users.

Side effects of the pill, which often subside after a few months' use, include nausea, headache, breast tenderness, weight gain, irregular bleeding, and depression.

Doctors sometimes prescribe higher doses of combined oral contraceptives for use as "morning after" pills to be taken within 72 hours of unprotected intercourse to prevent the possibly fertilized egg from reaching the uterus. In a Feb. 25, 1997, *Federal Register* notice, FDA stated its conclusion that, on the basis of current scientific evidence, certain oral contraceptives are safe and effective for this use.

• ***Minipills.*** Although taken daily like combined oral contraceptives, minipills contain only the hormone progestin and no estrogen. They work by reducing and thickening cervical mucus to prevent sperm from reaching the egg. They also keep the uterine lining from thickening, which prevents a fertilized egg from implanting in the uterus. These pills are slightly less effective than combined oral contraceptives.

Minipills can decrease menstrual bleeding and cramps, as well as the risk of endometrial and ovarian cancer and pelvic inflammatory disease. Because they contain no estrogen, minipills don't

"In the population for which the IUD is appropriate—for those in a mutually monogamous, stable relationship who aren't at a high risk of infection—the IUD is a very safe and very effective method of contraception."

—Lisa Rarick, M.D., director of FDA's division of reproductive and urologic drug products

present the risk of blood clots associated with estrogen in combined pills. They are a good option for women who can't take estrogen because they are breast-feeding or because estrogen-containing products cause them to have severe headaches or high blood pressure.

Side effects of minipills include menstrual cycle changes, weight gain, and breast tenderness.

• ***Injectable progestins.*** Depo-Provera, approved by FDA in 1992, is injected by a health professional into the buttocks or arm muscle every three months. Depo-Provera prevents pregnancy in three ways: It inhibits ovulation, changes the cervical mucus to help prevent sperm from reaching the egg, and changes the uterine lining to prevent the fertilized egg from implanting in the uterus. The progestin injection is extremely effective in preventing pregnancy, in large part because it requires little effort for the woman to comply: She simply has to get an injection by a doctor once every three months.

The benefits are similar to those of the minipill and another progestin-only contraceptive, Norplant. Side effects are also similar and can include irregular or missed periods, weight gain, and breast tenderness.

(See "Depo-Provera: The Quarterly Contraceptive" in the March 1993 *FDA Consumer*.)

• ***Implantable progestins.*** Norplant, approved by FDA in 1990, and the newer Norplant 2, approved in 1996, are the third type of progestin-only contraceptive. Made up of matchstick-sized rubber rods, this contraceptive is surgically implanted under the skin of the upper arm, where it steadily releases the contraceptive steroid levonorgestrel.

The six-rod Norplant provides protection for up to five years (or until it is removed), while the two-rod Norplant 2 protects for up to three years. Norplant failures are rare, but are higher with increased body weight.

Some women may experience inflammation or infection at the site of the implant. Other side effects include menstrual cycle changes, weight gain, and breast tenderness.

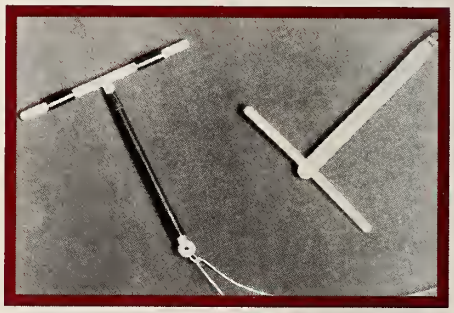
Intrauterine Devices

An IUD is a T-shaped device inserted into the uterus by a health-care professional. Two types of IUDs are available in the United States: the Paragard CopperT 380A and the Progestasert Progesterone T. The Paragard IUD can remain in place for 10 years, while the Progestasert IUD must be replaced every year.

It's not entirely clear how IUDs prevent pregnancy. They seem to prevent sperm and eggs from meeting by either immobilizing the sperm on their way to the fallopian tubes or changing the uterine lining so the fertilized egg cannot implant in it.

IUDs have one of the lowest failure rates of any contraceptive method. "In the population for which the IUD is appropriate—for those in a mutually monogamous, stable relationship who aren't at a high risk of infection—the IUD is a very safe and very effective method of contraception," says Lisa Rarick, M.D., director of FDA's division of reproductive and urologic drug products.

The IUD's image suffered when the Dalkon Shield IUD was taken off the market in 1975. This IUD was associated with a high incidence of pelvic infections and infertility, and some deaths.



Today, serious complications from IUDs are rare, although IUD users may be at increased risk of developing pelvic inflammatory disease. Other side effects can include perforation of the uterus, abnormal bleeding, and cramps. Complications occur most often during and immediately after insertion.

Traditional Methods

• ***Fertility awareness.*** Also known as natural family planning or periodic abstinence, fertility awareness entails not having sexual intercourse on the days of a woman's menstrual cycle when she could become pregnant or using a barrier method of birth control on those days.

Because a sperm may live in the female's reproductive tract for up to seven days and the egg remains fertile for about 24 hours, a woman can get

pregnant within a substantial window of time—from seven days before ovulation to three days after. Methods to approximate when a woman is fertile are usually based on the menstrual cycle, changes in cervical mucus, or changes in body temperature.

"Natural family planning can work,"

Being informed about the pros and cons of various contraceptives is important not only for preventing unintended pregnancies but also for reducing the risk of illness or death from sexually transmitted diseases, including AIDS.

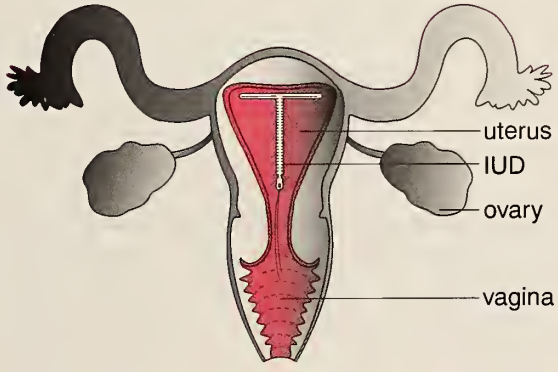
Birth Control In the Body

Site of Norplant Insertion

(After insertion beneath the skin, the device is not visible.)

Insertion of Female Condom

IUD in Position



Rarick says, "but it takes an extremely motivated couple to use the method effectively."

• ***Withdrawal.*** In this method, also called *coitus interruptus,* the man withdraws his penis from the vagina before ejaculation. Fertilization is prevented because the sperm don't enter the vagina.

Effectiveness depends on the male's ability to withdraw before ejaculation. Also, withdrawal doesn't provide protection from STDs, including HIV. Infectious diseases can be transmitted by direct contact with surface lesions and by pre-ejaculatory fluid.

Surgical Sterilization

Surgical sterilization is a contraceptive option intended for people who don't want children in the future. It is considered permanent because reversal requires major surgery that is often unsuccessful.

• ***Female sterilization.*** Female sterilization blocks the fallopian tubes so the egg can't travel to the uterus. Sterilization is done by various surgical techniques usually under general anesthesia.

Complications from these operations are rare and can include infection, hemorrhage, and problems related to the use of general anesthesia.

• ***Male sterilization.*** This procedure, called a vasectomy, involves sealing, tying or cutting a man's vas deferens, which otherwise would carry the sperm from the testicle to the penis.

Vasectomy involves a quick operation, usually under 30 minutes, with possible minor postsurgical complications, such as bleeding or infection.

Research continues on effective contraceptives that minimize side effects. One important research focus, according to FDA's Rarick, is the development of birth control methods that are both spermicidal and microbicidal to prevent not only pregnancy but also transmission of HIV and other STDs. ■

Tamar Nordenberg is a staff writer for FDA Consumer.

Birth Control Guide

Efficacy rates in this chart are based on *Contraceptive Technology* (17th edition). They are yearly estimates of effectiveness in typical use, which refers to a method's reliability in real life, when people don't always use a method properly. For comparison, about 85 percent of sexually active women using no contraception would be expected to become pregnant in a year.

This chart is a summary; it is not intended to be used alone. All product labeling should be followed carefully, and a health-care professional should be consulted for some methods.

Type	**Male Latex Condom**[a]	**Female Condom**	**Diaphragm with Spermicide**	**Cervical Cap with Spermicide**	**Sponge with Spermicide** (not currently marketed)	**Spermicides Alone**
Estimated Effectiveness	86%	79%	80%	60–80%[b]	60–80%[b]	74%
Some Risks[c]	Irritotion and allergic reoctions (less likely with palyurethane)	Irritotion ond ollergic reoctions	Irritotian ond allergic reactions, urinory tract infectian	Irritatian and allergic reoctions, obnarmol Pap test	Irritatian and allergic reactians, difficulty in remavol	Irritatian and allergic reactians
Protection from Sexually Transmitted Diseases (STDs)	Except far abstinence, lotex condoms ore the best protection against STDs, including herpes and AIDS.	Moy give same STD protectian; nat as effective os lotex candom.	Pratects against cervicol infectian; spermicide may give same pratection against chlamydio ond gonarrhea; otherwise unknawn.	Spermicide may give same pratection against chlamydio ond gonarrhea; otherwise unknown.	Spermicide moy give some protectian agoinst chlamydia and gonorrheo; atherwise unknown.	May give same pratection agoinst chlamydio ond ganarrhea; atherwise unknawn.
Convenience	Applied immediotely before intercaurse; used only once ond discorded.	Applied immediately before intercourse; used only once ond discorded.	Inserted before intercourse ond left in ploce ot leost six hours ofter; con be left in ploce far 24 hours, with odditionol spermicide for repeoted intercourse.	May be difficult to insert; can remain in place far 48 haurs without reapplying spermicide far repeoted intercaurse.	Inserted before intercaurse and protects far 24 hours withaut additianal spermicide; must be left in place far at leost six haurs after intercourse; must be remaved within 30 hours of insertian; used anly ance and discarded.	Instructians vary; usually applied no mare than ane haur before intercaurse ond left in place ot leost six ta eight hours after.
Availability	Nanprescription	Nonprescriptian	Prescription	Prescription	Nonprescriptian; not currently marketed.	Nanprescriptian

a Effectiveness rate for polyurethane condoms has not been established.
b Less effective for women who have had a baby because the birth process stretches the vagina and cervix, making it more difficult to achieve a proper fit.
c Serious medical risks from contraceptives are rare.

Oral Contraceptives—combined pill	Oral Contraceptives—progestin-only minipill	Injection (Depo-Provera)	Implant (Norplant)	IUD (Intrauterine Device)	Periodic Abstinence	Surgical Sterilization—female or male
95%	95%	Over 99%	Over 99%	98–99%	About 75% (varies, based on method)	Over 99%
Dizziness; nausea; changes in menstruation, mood, and weight; rarely, cardiovascular disease, including high blood pressure, blood clots, heart attack, and strokes	Irregular bleeding, weight gain, breast tenderness, less protection against ectopic pregnancy	Irregular bleeding, weight gain, breast tenderness, headaches	Irregular bleeding, weight gain, breast tenderness, headaches, difficulty in removal	Cramps, bleeding, pelvic inflammatory disease, infertility, perforation of uterus	None	Pain, bleeding, infection, other minor postsurgical complications
None, except some protection against pelvic inflammatory disease.	None, except some protection against pelvic inflammatory disease.	None	None	None	None	None
Must be taken on daily schedule, regardless of frequency of intercourse.	Must be taken on daily schedule, regardless of frequency of intercourse.	One injection every three months	Implanted by health-care provider—minor outpatient surgical procedure; effective for up to five years.	After insertion by physician, can remain in place for up to one or 10 years, depending on type.	Requires frequent monitoring of body functions (for example, body temperature for one method).	One-time surgical procedure
Prescription	Prescription	Prescription	Prescription	Prescription	Instructions from health-care provider	Surgery

Preventing HIV And Other STDs

Some people mistakenly believe that by protecting themselves against pregnancy, they are automatically protecting themselves from HIV, the virus that causes AIDS, and other sexually transmitted diseases (STDs). But the male latex condom is the only contraceptive method considered highly effective in reducing the risk of STDs.

Unlike latex condoms, lambskin condoms are not recommended for STD prevention because they are porous and may permit passage of viruses like HIV, hepatitis B and herpes. Polyurethane condoms are an alternative method of STD protection for those who are latex-sensitive.

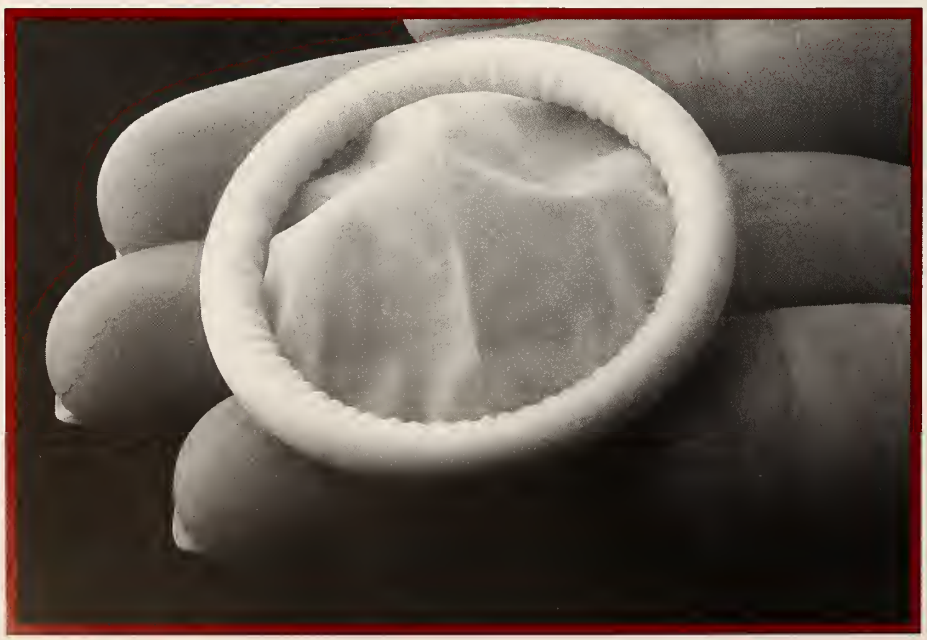
Because it is a barrier method that works in much the same way as the male condom, the female condom may provide some protection against STDs. Both condoms should not be used together, however, because they may not both stay in place.

According to an FDA advisory committee panel that met Nov. 22, 1996, it appears, based on several published scientific studies, that some vaginal spermicides containing nonoxynol-9 may reduce the risk of gonorrhea and chlamydia transmission. However, use of nonoxynol-9 may cause tissue irritation, raising the possibility of an increased susceptibility to some STDs, including HIV.

As stated in their labeling, birth control pills, Norplant, Depo-Provera, IUDs, and lambskin condoms do not protect against STD infection. For STD protection, a male latex condom can be used in combination with these non-condom methods. The relationship of the vaginal barrier methods—the diaphragm, cap and sponge—to STD prevention is not yet clear. ■

—T.N.

Except for abstinence, latex condoms are the most effective method for reducing the risk of infection from the viruses that cause AIDS, other HIV-related illnesses, and other sexually transmitted diseases.



Overcoming Infertility

by Tamar Nordenberg

Image provided by © 1994 PhotoDisc, Inc.

Myth or fact: If a couple is having trouble conceiving a child, the man should try wearing loose underwear? That's a fact, according to a study on "Tight-fitting Underwear and Sperm Quality" published June 29, 1996, in the scientific journal *The Lancet.* Tight-fitting underwear—as well as hot tubs and saunas—is not recommended for men trying to father a child because it may raise testes temperature to a point where it interferes with sperm production.

But couples having difficulty getting pregnant can tell you the solution is almost never as simple as wearing boxers instead of briefs. Lisa (who asked that her last name not be used) tried for more than two years to get pregnant without success. "Everyone gave me advice," she says. "My mother said I should just go to church and pray more. My friends said, 'Try to relax and not think about it' or 'You're just overstressed. You work too much.' "

Actually, psychological stress is more likely a *result* of infertility than the cause, according to Resolve, a nonprofit consumer organization specializing in infertility.

"Fertility problems are a huge psychological stressor, a huge relationship stressor," says Lisa Rarick, M.D., director of the Food and Drug Administration's division of reproductive and urologic drug products.

So, while going on a relaxing vacation may temporarily relieve the stress that comes with fertility problems, a solution may require treatment by a health-care professional. Treatment with drugs such as Clomid or Serophene (both clomiphene citrate) or Pergonal, Humegon, Metrodin, Repronal or Fertinex (all menotropins) are used in some cases to correct a woman's hormone imbalance. (See "Drug Supply Restored.") Surgery is sometimes used to repair damaged reproductive organs. And in about 10 percent of cases, less conventional, high-tech options like *in vitro* fertilization are used.

Will the therapies work? "Talking about the success rate for fertility treatments is like saying, 'What's the chance of curing a headache?' " according to Benjamin Younger, M.D., executive director of the American Society for Reproductive Medicine. "It depends on many things, including the cause of the problem and the severity." Overall, Younger says, about half of couples that seek fertility treatment will be able to have babies.

A Year Without Pregnancy

Infertility is defined as the inability to conceive a child despite trying for one year. The condition affects about 5.3 million Americans, or 9 percent of the reproductive age population, according to the American Society for Reproductive Medicine.

Ironically, the best protection against infertility is to use a condom while you are not trying to get pregnant. Condoms prevent sexually transmitted diseases, a primary cause of infertility.

Even a completely healthy couple can't expect to get pregnant at the drop of a hat. Only 20 percent of women who want to conceive become pregnant in the first ovulation cycle they try, according to Younger.

To become pregnant, a couple must have intercourse during the woman's fertile time of the month, which is right before and during ovulation. Because it's tough to pinpoint the exact day of ovulation, having intercourse often during the approximate time maximizes the chances of conception.

After a year of frequent intercourse without contraception that doesn't result in pregnancy, a couple should go to a health-care professional for an evaluation. In some cases, it makes sense to seek help for fertility problems even before a year is up.

A woman over 30 may wish to get an earlier evaluation. "At age 30, a woman begins a slow decline in her ability to get pregnant," says Younger. "The older she gets, the greater her chance of miscarriage, too." But a woman's fertility doesn't take a big drop until around age 40.

"A man's age affects fertility to a much smaller degree and 20 or 30 years later than in a woman," Younger says. Despite a decrease in sperm production that begins after age 25, some men remain fertile into their 60s and 70s.

A couple may also seek earlier evaluation if:

- The woman isn't menstruating regularly, which may indicate an absence of ovulation that would make it impossible for her to conceive without medical help.
- The woman has had three or more miscarriages (or the man had a previous partner who had had three or more miscarriages).
- The woman or man has had certain infections that sometimes affect fertility (for example, pelvic infection in a woman, or mumps or prostate infection in a man).
- The woman or man suspects there may be a fertility problem (if, for example, attempts at pregnancy failed in a previous relationship).

The Man or the Woman?

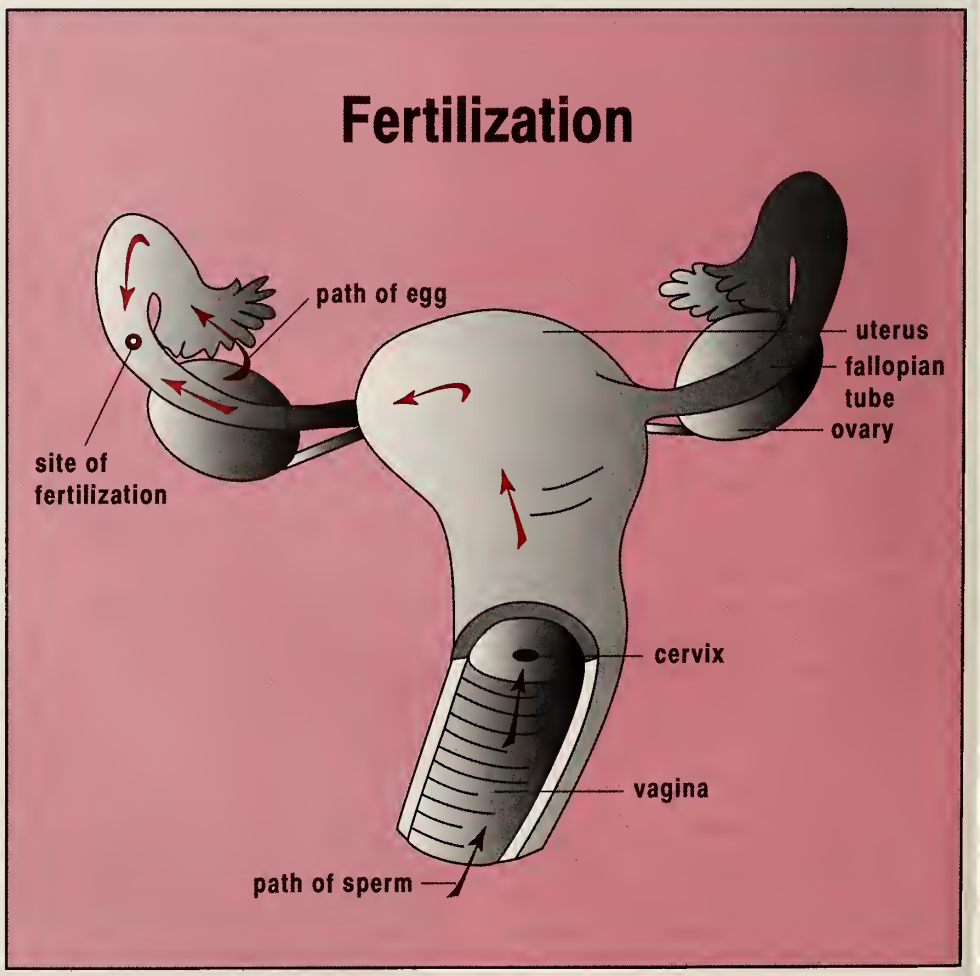
Impairment in any step of the intricate process of conception can cause infertility. For a woman to become pregnant, her partner's sperm must be healthy so that at least one can swim into her fallopian tubes. An egg, released by the woman's ovaries, must be in the fallopian tube ready to be fertilized. (See diagram below.) Next, the fertilized egg, called an embryo, must make its way through an open-ended fallopian tube into the uterus, implant in the uterine lining, and be sustained there while it grows.

It is a myth that infertility is always a "woman's problem." Of the 80 percent of cases with a diagnosed cause, about half are based at least partially on male problems (referred to as male factors)—usually that the man produces no sperm, a condition called azoospermia, or that he produces too few sperm, called oligospermia.

Lifestyle can influence the number and quality of a man's sperm. Alcohol and drugs—including marijuana, nicotine, and certain medications—can temporarily reduce sperm quality. Also, environmental toxins, including pesticides and lead, may be to blame for some cases of infertility.

The causes of sperm production problems can exist from birth or develop later as a result of severe medical illnesses, including mumps and some sexually transmitted diseases, or from a severe testicle injury, tumor, or other problem. Inability to ejaculate normally can prevent conception, too, and can be caused by many factors, including diabetes, surgery of the prostate gland or urethra, blood pressure medication, or impotence.

The other half of explained infertility



Science and ART

Sometimes it may be necessary or preferable to get pregnant without intercourse. A woman may choose to get pregnant with the sperm of someone who is not her partner.

In some cases, a woman may not be able to become pregnant with her partner because his sexual problems make it impossible for him to ejaculate normally during sex, or because the sperm have to bypass the vagina if the vaginal mucus cannot support them, or for other reasons. In these cases, through artificial insemination, the semen is placed into the woman's uterus or vaginal canal using a hollow, flexible tube called a catheter.

New, more complex assisted reproductive technologies, or ART, procedures, including *in vitro* fertilization (IVF), have been available since the birth 18 years ago of Louise Brown, the world's first "test tube baby." IVF makes it possible to combine sperm and eggs in a laboratory for a baby that is genetically related to one or both partners.

IVF is often used when a woman's fallopian tubes are blocked. First, medication is given to stimulate the ovaries to produce multiple eggs. Once mature, the eggs are suctioned from the ovaries and placed in a laboratory culture dish with the man's sperm for fertilization. About two days later, three to five embryos are transferred to the woman's uterus. If the woman does not become pregnant, she may try again in the next cycle.

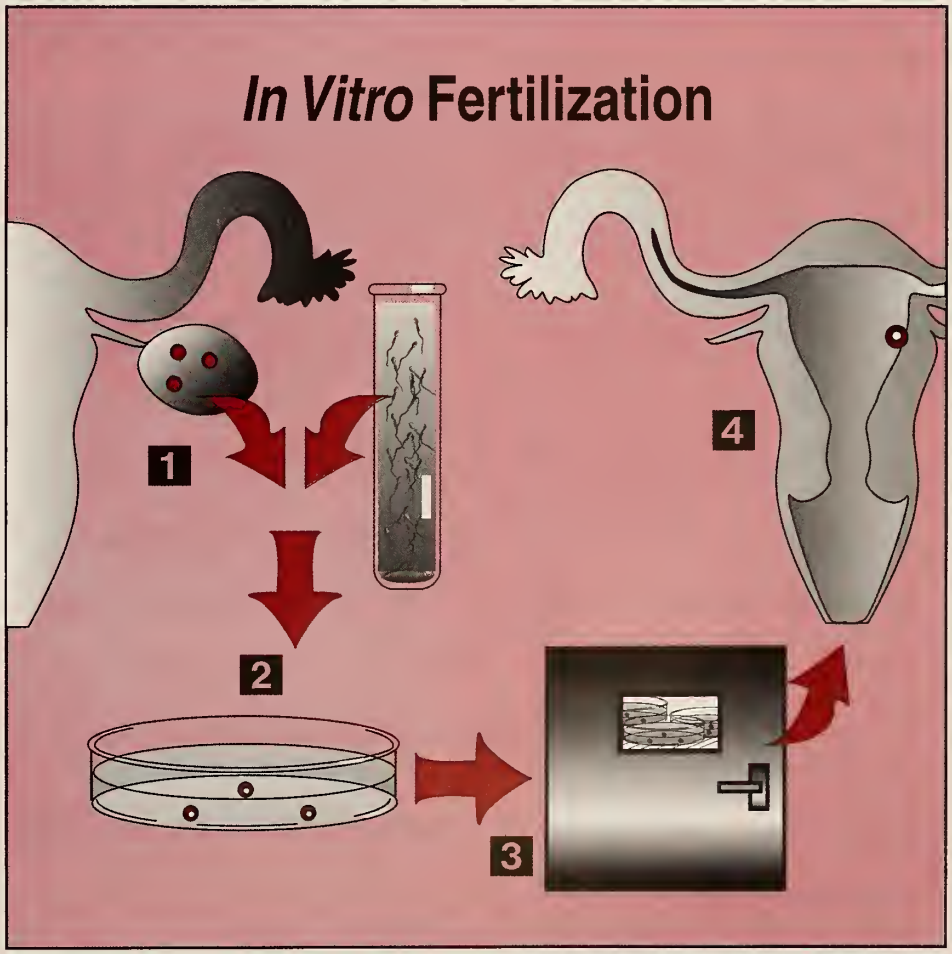
Other ART procedures, based on many of the same principles, include:

- ***Gamete intrafallopian transfer, or GIFT:*** Similar to IVF, but used when the woman has at least one normal fallopian tube. Three to five eggs are placed in the fallopian tube, along with the man's sperm, for fertilization inside the woman's body.
- ***Zygote intrafallopian transfer, or ZIFT*** (also called tubal embryo transfer): A hybrid of IVF and GIFT. The eggs retrieved from the woman's ovaries are fertilized in the lab and replaced in the fallopian tubes rather than the uterus.
- ***Donor egg IVF:*** For women who, for example, have impaired ovaries or carry a genetic disease that can be transferred to the offspring. Eggs are donated by another healthy woman and fertilized in the lab with the male partner's sperm before being transferred to the female partner's uterus.
- ***Frozen embryos:*** Excess embryos are frozen, to be thawed in the future if the woman doesn't get pregnant on the first cycle or wants another baby in the future.

New treatments for male factors are fast-evolving. Intracytoplasmic sperm injection is one of the most exciting new procedures, according to Benjamin Younger, M.D., executive director of the American Society for Reproductive Medicine. A single egg is injected with a single sperm to produce an embryo that can implant and grow in the uterus.

About two-thirds of births from ART procedures are single births. Of the rest, almost all are twins, with about 6 percent resulting in the birth of triplets or more. ■

—T.N.



1 The eggs are removed from the ovary.
2 The eggs and sperm from a donor are combined in a Petri dish.
3 The Petri dish is placed in an incubator.
4 If fertilization occurs, the embryo is transferred to the uterus.

cases are linked to female problems (called female factors), most commonly ovulation disorders. Without ovulation, eggs are not available for fertilization. Problems with ovulation are signaled by irregular menstrual periods or a lack of periods altogether (called amenorrhea). Simple lifestyle factors—including stress, diet, or athletic training—can affect a woman's hormonal balance. Much less often, a hormonal imbalance can result from a serious medical problem such as a pituitary gland tumor.

Other problems can also lead to female infertility. If the fallopian tubes are blocked at one or both ends, the egg can't travel through the tubes into the uterus. Such blockage may result from pelvic inflammatory disease, surgery for an ectopic pregnancy (when the embryo implants in the fallopian tube rather than in the uterus), or other problems, including endometriosis (the abnormal presence of uterine lining cells in other pelvic organs).

A medical evaluation may determine whether a couple's infertility is due to these or other causes. If a medical and sexual history doesn't reveal an obvious problem, like improperly timed intercourse or absence of ovulation, specific tests may be needed.

Tests for Both

The man's evaluation focuses on the number and health of his sperm. The laboratory first examines a sperm sample under a microscope to check sperm number, shape and movement. Further tests may be needed to look for infection, hormonal imbalance, or other problems.

Male tests include:

- *X-ray:* If damage to one or both of the vas deferens (the ducts in the male that transport the sperm to the penis) is known or suspected, an x-ray is taken to examine the organs.
- *Mucus penetrance test:* Test of whether the man's sperm are able to swim through a drop of the woman's fertile vaginal mucus on a slide (also used to test the quality of the woman's mucus).
- *Hamster-egg penetrance assay:* Test of whether the man's sperm will penetrate hamster egg cells with their outer cells removed, indicating somewhat their ability to fertilize human eggs.

It is a myth that infertility is always a "woman's problem."

For the woman, the first step in testing is to determine if she is ovulating each month. This can be done by charting changes in morning body temperature, by using an FDA-approved home ovulation test kit (which is available over the counter), or by examining cervical mucus, which undergoes a series of hormone-induced changes throughout the menstrual cycle.

Checks of ovulation can also be done in the physician's office with simple blood tests for hormone levels or ultrasound tests of the ovaries. If the woman is ovulating, further testing will need to be done.

Common female tests include:

- *Hysterosalpingogram:* An x-ray of the fallopian tubes and uterus after they are injected with dye, to show if the tubes are open and to show the shape of the uterus.
- *Laparoscopy:* An examination of the tubes and other female organs for disease, using a miniature light-transmitting tube called a laparoscope. The tube is inserted into the abdomen through a one-inch incision below the navel, usually while the woman is under general anesthesia.
- *Endometrial biopsy:* An examination of a small shred of uterine lining to see if the monthly changes in the lining are normal.

Some tests require participation of both partners. Samples of cervical mucus taken after intercourse can show whether sperm and mucus have properly interacted. Also, a variety of tests can show if the man or woman is forming antibodies that are attacking the sperm.

Drugs and Surgery

Depending on what the tests turn up, different treatments are recommended. Eighty to 90 percent of infertility cases are treated with drugs or surgery.

Therapy with the fertility drug Clomid or with a more potent hormone stimulator—Pergonal, Metrodin, Humegon or Fertinex—is often recommended for women with ovulation problems. The benefits of each drug and the side effects, which can be minor or serious but rare, should be discussed with the doctor. Multiple births occur in 10 to 20 percent of births resulting from fertility drug use.

Other drugs, used under very limited circumstances, include Parlodel (bromocriptine mesylate), for women with elevated levels of a hormone called prolactin, and a hormone pump that releases gonadotropins necessary for ovulation.

If drugs aren't the answer, surgery may be. Because major surgery is involved, operations to repair damage to the woman's ovaries, fallopian tubes, or uterus are recommended only if there is a good chance of restoring fertility.

In the man, one infertility problem often treated surgically is damage to the vas deferens, commonly caused by a sexually transmitted disease, other infection, or vasectomy (male sterilization).

Other important tools in the battle against infertility include artificial insemination and the so-called assisted reproductive technologies. (See "Science and Art.")

Fulfillment Regardless

Lisa became pregnant without assisted reproductive technologies, after taking ovulation-promoting medication and undergoing surgery to repair her damaged fallopian tubes. Her daughter is now 4 years old.

"It was definitely worth it. I really appreciate having my daughter because of what I went through," she says. But Lisa and her husband won't try to have a second child just yet. "At some point you have to stop trying to have a baby, stop obsessing over what might be an

Drug Supply Restored

The availability of sufficient supplies of the FDA-approved fertility drugs Pergonal, Metrodin, and Humegon and the recent FDA approvals of the fertility drugs Fertinex and Repronal have ended a shortage of these types of drugs in the United States. Since the drugs are not in short supply anymore, FDA will no longer allow the importation of unapproved versions of fertility drugs, even for personal use.

In February 1995, FDA became aware of a shortage of the approved fertility drugs Pergonal and Metrodin, both manufactured by Serono Laboratories Inc. of Switzerland.

Because of the shortage, FDA has allowed people to temporarily import unapproved foreign versions of fertility drugs for their own use. "FDA used its enforcement discretion to allow the importation of unapproved versions of fertility drugs on a personal use basis," says Thomas Gardine, director of the agency's division of import operations and policy.

FDA asked doctors to wait until the supply of approved drugs increased unless a patient was in the midst of therapy. "There's always a danger in taking unapproved drugs because they are of unknown quality and haven't been shown to FDA to be safe, effective, and adequately labeled," Gardine says.

The Serono manufacturing plant in Switzerland is again supplying adequate amounts of Pergonal and Metrodin for U.S. patients. Also, other products are now available for the same use.

"The drug shortage no longer exists to merit our allowing importation of the unapproved products," Gardine says. After a reasonable time to make the public aware of the change in FDA's position, the agency will no longer allow the unapproved versions of these drugs to enter the country.

The following fertility drugs are approved by FDA and can be obtained with a doctor's prescription:

Trade Name[1]	Chemical Name	Manufacturer	Telephone No.
Clomid	clomiphene citrate	Hoechst Marion Roussel	(816) 966-5170
Serophene	clomiphene citrate	Serono	(800) 283-8088
Clomiphene citrate	clomiphene citrate	Milex	(312) 631-6484
Pergonal	menotropins	Serono	(800) 283-8088
Humegon	menotropins	Organon	(800) 631-1253
Repronal	menotropins	Ferring	(914) 333-8947
Metrodin	urofollitropin	Serono	(800) 283-8088
Fertinex	urofollitropin highly purified	Serono	(800) 283-8088
Chorionic gonadotropin	chorionic gonadotropin[2]	Steris	(602) 278-1400
A.P.L.	chorionic gonadotropin[2]	Wyeth Ayerst	(601) 341-2239
Chorionic gonadotropin	chorionic gonadotropin[2]	Fujisawa	(847) 317-8800
Pregnyl	chorionic gonadotropin[2]	Organon	(800) 631-1253

[1] Some of these drug products may be sold under other brand names by distributors who buy the products from the listed manufacturers.

[2] Chorionic gonadotropin is not normally used alone as a fertility drug—it is normally administered after administration of menotropins or urofollitropin.

unreachable goal," she says.

When having a genetically related baby seems unachievable, a couple may decide to stop treatment and proceed with the rest of their lives. Some may choose to lead an enriched life without children. Others may choose to adopt.

And no, according to Resolve, you're not more likely to get pregnant if you adopt a baby.

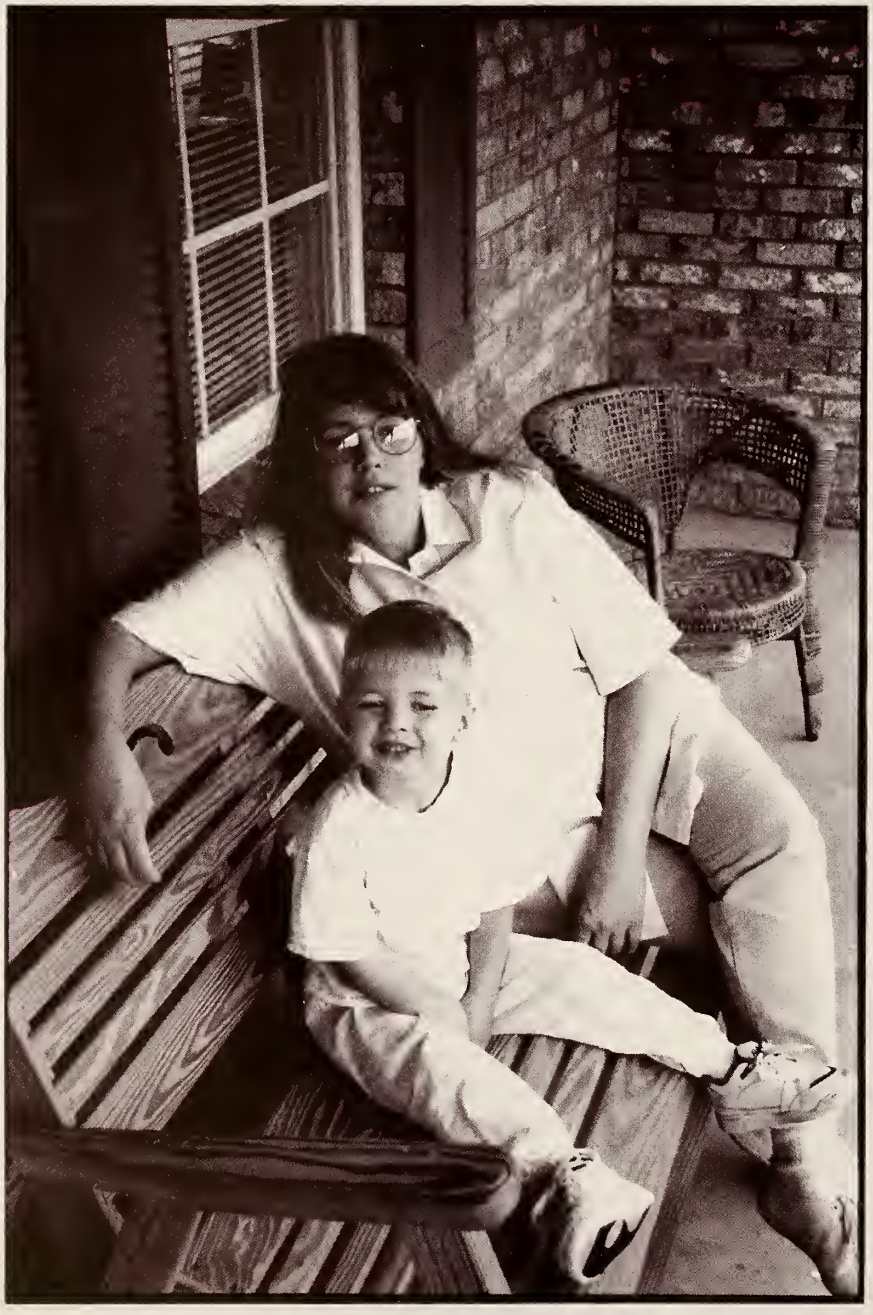
To get more information about infertility, send a self-addressed, stamped envelope to: Resolve, 1310 Broadway, Somerville, MA 02144-1731; call their National Helpline at (617) 623-0744; or visit their World Wide Web site at *http://www.resolve.org/*. ■

Tamar Nordenberg is a staff writer for FDA Consumer.

Decreasing The Chance Of

Birth Defects

by Rebecca D. Williams



Tammy Troutman, born with spina bifida, sits on the porch of her Knoxville home with her son, Evan, 3. Troutman took prenatal precautions, and Evan was born with a normal spine.

PHOTO BY GARY TROUTMAN

Most birth defects occur in the first three months of pregnancy, when the organs are forming.

When Tammy Troutman of Knoxville, Tenn., was planning her first pregnancy, she had a good reason to be concerned about birth defects.

Born with a mild form of spina bifida, Troutman worried her child would also have the condition. So she did what health-care experts say is the best first step toward preventing birth defects: She visited her physician for an exam well before she and her husband tried to conceive.

"Before I decided to have children, I went to the doctor to make sure everything would be OK," Troutman remembers.

He advised her to take a daily multivitamin supplement containing folic acid, a B vitamin that would decrease her chances of having a baby with spina bifida. Troutman took the vitamins for five months before conceiving her son, Evan, who was born in August 1993 with a normal, healthy spine.

"Even if he had been born with spina bifida," Troutman says, "I felt secure knowing that I had done everything I could to prevent it."

Of the 4 million infants born annually in the United States, about 3 to 5 percent are born with birth defects, according to the March of Dimes. Birth defects account for 20 percent of all infant deaths in the United States, more than from any other single cause.

"For the majority of birth defects, the cause is unknown," says Franz Rosa, M.D., a pediatrician, formerly with the Food and Drug Administration, who monitored reports of prescription drugs causing birth defects. Rosa cites a list of drugs that are known to be birth-defect causing, but he says they only account for a small percentage of all malformations.

"There's a lot we just don't know," Rosa says. "Most birth defects are not preventable and mothers should not feel guilty about causing defects that they really didn't. Worrying too much is not good for pregnancies."

What experts do know is that most birth defects occur in the first three months of pregnancy, when the organs are forming. It is in these crucial first few weeks—often before a woman even knows she's pregnant—that an embryo is most susceptible to teratogens, substances that can cause defects. However, some birth defects do occur later in pregnancy as well.

"The key is what your life is like at the time you become pregnant," says Deborah Smith, M.D., an obstetrician and gynecologist in FDA's Office of Women's Health. "Are you getting

One nutrient known to prevent birth defects is folic acid.

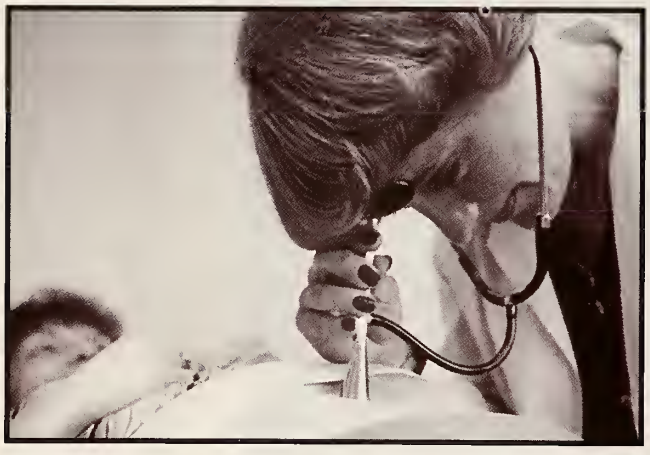


Image provided by © 1994 PhotoDisc, Inc.

enough folic acid, are you immune to rubella, are you avoiding alcohol and smoking? These are some of the things we know are important."

Despite the benefits of seeing a doctor before conceiving, only 26 percent of women planning a pregnancy do so, according to the March of Dimes. Furthermore, health experts estimate more than 50 percent of pregnancies are unplanned. That's why a healthy lifestyle for all women who could become pregnant—even if they don't intend to—is the best way to minimize the risk of birth defects.

Healthy Diet

The maxim "You are what you eat" is sterling advice during the first three months of pregnancy.

Studies of women who had endured starvation during World War II illustrate the importance of diet early in pregnancy. Contrary to what researchers expected, it was not the babies *born* during food deprivation that had the most malformations, but those *conceived* during food deprivation.

One nutrient known to prevent birth defects is folic acid, the B vitamin Tammy Troutman took before her pregnancy. Folic acid is the chemical form of folate, which is found in green leafy vegetables, citrus fruits, and legumes. Folate aids in cell division, and taking extra folic acid reduces a woman's chance of having a child with spina bifida and other abnormalities of the spine and brain.

Spina bifida occurs when the vertebrae do not close completely. It is one of several conditions known as neural tube defects, because the neural tube is the portion of the embryo that develops into the brain and spinal column. In very mild cases, spina bifida causes few or minor problems, but in more severe cases, the spinal cord protrudes through the vertebrae into a sac outside the child's body. This impairs the child's mobility and other neurological functions and requires surgery to repair the opening.

To help prevent neural tube defects, the U.S. Public Health Service has recommended that all women of childbearing age who are capable of becoming pregnant consume 0.4 milligrams (mg) of folic acid per day. (For pregnant or lactating women, the daily value increases to 0.8 mg per day.) It is especially important that women take in sufficient folate before they become pregnant.

FDA recently published regulations requiring manufacturers to add folic acid to enriched grain products such as flour, noodles, bread, rolls, buns, farina, cornmeal, grits, and rice by January 1998.

Although the main challenge in pregnancy is getting enough nutrients, too much of a good thing is not good for a developing baby, either. Vitamins A and D are the most notable examples. Both can be toxic at levels higher than the recommended daily allowance. Such levels are rarely reached through food intake; however, women taking dietary supplements need to be aware of this risk and the amount of these vitamins they are taking. Women who take vitamin and mineral supplements should discuss with a health-care professional what vitamins are safe to continue taking during pregnancy.

Only a few foods are completely off-limits during pregnancy. These include raw or undercooked meat, such as "pink-in-the-middle" burgers, and raw or undercooked seafood. Bacteria from these can cause severe food poisoning, which is dangerous to a fetus and very unpleasant for the mother.

Soft drinks, coffee, tea, and other caffeinated drinks can be used in moderation. Although large doses of caffeine have caused skeletal defects in rats, one or two cups of coffee daily are not considered dangerous for developing fetuses.

Alcohol should be avoided at all times during pregnancy because it leads to low birth weight and can cause deformities as well.

According to the March of Dimes, alcohol is the most common known cause

Accutane and Birth Defects

Accutane (isotretinoin), a relative of vitamin A, is approved to treat severe cystic acne that doesn't respond to other drugs. It has some serious side effects, though, especially if a woman taking it becomes pregnant.

The drug's manufacturer has included strong warnings in the package labeling to inform doctors and patients about the birth defects this drug can cause.

Pregnant women who take Accutane even for a short time are at great risk of having a baby with severe facial birth defects, malformed thymus glands, and mental retardation.

The risk is so great that any woman of childbearing age who is taking Accutane—even if she's not sexually active—must also use effective contraception at least one month before beginning Accutane, while using the drug, and for one month after stopping. ■

—R.D.W.

of fetal damage in the country and the leading cause of preventable mental retardation. Pregnant women who drink alcohol, especially in large amounts, put their babies at risk for fetal alcohol syndrome, which causes growth retardation, facial deformities such as a small head, thin upper lip, and small jaw bone, an underdeveloped thymus gland, and mental deficiencies or developmental delays.

If a woman has had a glass or two of wine before finding out she was pregnant, she probably has not harmed her child. But since no one knows the exact amount of alcohol that is dangerous, it's best to avoid alcohol when pregnancy is possible.

Healthy Mothers, Healthy Babies

A pregnant woman who has a serious medical condition may face a greater than normal risk that her child will have a birth defect.

Diabetes, for example, can complicate a pregnancy in many ways. Women who must take insulin daily to control their blood sugar are three or four times more likely to have a baby with major birth defects than are other mothers. That's not to say they should abandon insulin, however. Without it, many diabetic women and their babies wouldn't survive pregnancy at all.

Birth defects among diabetics can be greatly reduced if women get their blood sugar levels under control before becoming pregnant and strictly manage their diets throughout pregnancy. Gestational diabetes, which develops during pregnancy, can also be harmful to mother and child, but it can be controlled through diet or medication.

Epilepsy also increases a woman's chance of having a baby with a birth defect. It's not clear whether the disease itself or the drugs used to control it cause malformations, but in either case, the woman's neurologist and obstetrician should work together to find the safest course of treatment for the epilepsy and pregnancy.

Rubella, toxoplasmosis, cytomegalovirus, and syphilis can cause birth defects in the infants of women who have these infectious diseases. Rubella infection during early pregnancy can cause abnormalities of the heart, eyes and ears. Any woman planning a pregnancy should be tested for rubella immunity and vaccinated if necessary. She must wait three months after vaccination before becoming pregnant, however, because the vaccine itself can endanger a developing fetus.

Toxoplasmosis is transmitted only through raw meat and cat feces, both of which pregnant women should try to avoid. The disease causes malformations of the brain, liver and spleen if a fetus becomes infected in the first trimester.

If a woman has syphilis, she should be treated with antibiotics before pregnancy. If not treated by at least the fourth month, syphilis can cause bone and tooth deformities in the baby, as well as nervous system and brain damage.

Cytomegalovirus (CMV) is a herpes virus that causes no real problem—and sometimes not even symptoms—for adults and children. In pregnancy, however, it can damage the fetus' brain, eyes

Alcohol should be avoided at all times during pregnancy because it leads to low birth weight and can cause deformities as well.

Image provided by © 1994 PhotoDisc, Inc.

or ears. Because most people contract the infection, whose symptoms are very much like a cold, when they are children, most adults are immune to it. Pregnant women who do not know if they've had CMV and who work with large groups of young children should discuss the situation with their health-care providers.

Sometimes it is not a disease that causes birth defects, but the medication used to treat it. Unfortunately, no one knows for certain how most drugs will affect a developing fetus. Historically, most women of childbearing age have been excluded from clinical trials of new drugs, and, although that is changing, drug manufacturers are understandably reluctant to involve pregnant women in clinical trials for new drugs. Therefore, the effects of many drugs are not known until they are in wider use after market approval.

To be on the safe side, a pregnant woman shouldn't take any drug unless it is absolutely necessary and not until she's checked with her health-care provider. However, even physicians have little information when prescribing medication for pregnant women. What is known about most drugs in pregnancy is based either on animal studies or on reports of problems after the drug is on the market. To give guidance about pregnancy safety, FDA requires that manufacturers include in the professional labeling for each drug which one of several categories, reflecting information from studies available at the time the label was developed.

Two examples: Taxol (paclitaxel), used to treat ovarian and breast cancer, may in some instances be appropriate in pregnancy even though it causes birth defects in animals and is therefore believed to cause fetal harm in humans. The benefits of its use to fight life-threatening cancers may outweigh the potential harm to a fetus.

Accutane (isotretinoin) should never be used in pregnancy. It is highly effective for treating severe cystic acne, but it causes serious birth defects. There are other drugs available to treat acne, and the disease is not life-threatening to the mother (see "Accutane and Birth Defects).

Who Should Paint the Nursery?

Chemicals—whether it's paint in the nursery or exhaust fumes in a parking garage—have long been suspected of causing birth defects. It's important for pregnant women to realize that most birth defects are not caused by a single factor, nor are they usually caused by faint traces of toxins. Scientists believe it takes a combination of factors to trigger a congenital malformation.

"Most birth defects have one or more genetic factors and one or more environmental factors," explains Richard Leavitt, director of science information at the March of Dimes.

Most of the chemicals a pregnant woman encounters pose little threat compared with the harm in smoking, drinking alcohol, or eating a poor diet.

"Most environmental exposure is at a low level compared to things you put in your mouth or inhale purposefully into your lungs," Leavitt says. "Public health warnings are aimed at the many to help the relatively few avoid a problem."

Daily, heavy exposure to chemicals may be dangerous, however. If a pregnant woman must work around fumes or chemicals, such as in a dry-cleaning business, art studio, or factory, she should use gloves, masks and adequate ventilation. But if she just gets a whiff of dry-cleaning fluid while picking up her laundry from the cleaners, there's little need to worry, Leavitt says.

Some environmental toxins such as lead are best avoided at any time, but especially during pregnancy. Scraping leaded paint off an old house window, drinking water from a pipe soldered with lead, or drinking out of decorative pottery containing lead can all potentially cause lead poisoning—and mental retardation—in a fetus. (See "Avoiding Lead.")

Avoiding Lead

FDA toxicologists agree that pregnant women should avoid daily drinking of hot coffee or tea or other hot acidic beverages, such as tomato soup, from lead-glazed ceramic cups or mugs. Hot acidic beverages such as coffee and tea, both caffeinated and decaffeinated, cause the greatest leaching of lead into the beverage. However, the occasional use of these pieces is not a problem, even during pregnancy.

The levels of lead in food and drink today are the lowest in history—90 percent lower than 15 years ago. This is mostly due to the U.S. food industry's voluntary elimination of lead solder to seal the seams of food cans and the removal of lead from automobile gasoline that settled on crops and in water.

But concern still remains about lead leaching into food from ceramic ware, especially mugs. While analyzing risks from dietary lead, FDA scientists found that about 80 percent of adult exposure to lead from food in contact with ceramic hollowware comes from frequent or daily use of mugs for hot beverages.

Consumers also need to be aware of the potential for lead to leach from ceramic plates, bowls and pitchers. Glaze, improperly formulated or fired, can leach large quantities of lead into food. Consumers who suspect a ceramic product has been improperly glazed or fired should avoid using it for food, or should test the piece for excessive lead leaching with commercially available kits before using it.

FDA advises consumers to avoid storing acidic beverages, such as fruit juices and iced tea, in lead-glazed pitchers because, even cold, acidic beverages have a greater tendency than other foods to cause leaching of lead.

In a final rule published in the *Federal Register* of Jan. 12, 1994, the agency amended its regulations to require that decorative ceramic products, which may leach hazardous amounts of lead into food, bear adequate indications that they are not to be used for holding, storing or serving food. This rule requires a permanent statement and a stick-on label on the exterior surface of any decorative ceramic product that the piece is not for food use, and that it may poison food. Alternatively, the rule provides that a hole may be bored through the possible food-contact surface of the piece.

Studies have also found that lead can leach into food from lead crystal hollowware. Pregnant women should not routinely drink from lead crystal glasses. Infants should not be fed with lead crystal baby bottles.

Lead can damage the developing fetus because it crosses the placental barrier.

In average adults, 10 to 15 percent of lead that reaches the digestive tract is absorbed. Young children and pregnant women, however, absorb as much as 50 percent. The body cannot distinguish between calcium and lead. Once lead enters the body, it is assimilated in the bloodstream in the same manner as calcium, and because young children and pregnant women absorb calcium more readily to meet their extra needs, they also absorb more lead. Those with calcium deficiencies absorb even more. And lead, even in small amounts, may become toxic wherever it settles.

Lead also gets into the blood of pregnant women from their own bone stores. During a period of physiological stress, such as in pregnancy or lactation, bone stores of minerals, including the normally inert lead, can be mobilized back into a woman's blood and increase her blood lead level. As this blood circulates, it is picked up by the fetus.

FDA toxicologists have set provisional total tolerable intake levels (PTTILs) of lead from all sources at 25 micrograms per day for pregnant women, and 6 micrograms per day for infants and children up to 6 years. For every microgram per day of lead intake, blood lead levels increase 0.16 micrograms per deciliter of blood in children and 0.04 micrograms per deciliter of blood in adults. ■

—Judith E. Foulke

Of the 4 million infants born annually in the United States, about 3 to 5 percent are born with birth defects.

Radiation is also dangerous to developing babies. A pregnant woman who works in an x-ray department of a hospital must take precautions to avoid exposure. Elective dental x-rays should be postponed until delivery, and any nonpregnant woman who has an x-ray should have her reproductive organs shielded with a lead apron.

Taking hot baths, using saunas, or exercising in hot, humid weather can raise a woman's core temperature and have the potential to cause birth defects, especially in the first trimester. Lukewarm baths and moderate exercise are fine, however.

And what about computers or video display terminals? Although they have at times been accused of causing harm, there's probably no need to worry. Recent studies have not found any relationship between computer terminals and miscarriages.

And as for who should paint the nursery—today's paints don't contain lead and therefore probably aren't dangerous. But there are other reasons to find someone else to do this task. The repetitive motion of painting can be a strain on back muscles already under pressure from the extra weight of pregnancy, and standing on your feet for hours can make advanced pregnancy miserable. If someone else can do it, pass this chore along.

Of all the environmental harms, undoubtedly the most harmful is one women can control—smoking. Although there is no evidence smoking causes birth defects, it deprives the fetus of oxygen and leads to a number of problems. If all pregnant women avoided smoking, the United States would see a 5 percent reduction in miscarriages, a 20 percent reduction in low-birth-weight births, and an 8 percent reduction in premature deliveries in this country, according to the March of Dimes.

In the Family

Finally, a number of birth defects are inherited. They are usually triggered when the child inherits a matching pair of disease-causing genes, one from each parent. This is most often an issue for couples of similar ethnic or geographic origins.

For example, African-American couples are most at risk for having a child with sickle cell anemia. According to the March of Dimes, couples of Ashkenazic Jewish or French Canadian descent may be carriers of Tay-Sachs disease. People who know of genetic disorders in their families, or those who have already had one child with a disorder are also at a greater risk, as are couples who are closely related, such as first cousins. Genetic testing is available to determine the risk of passing some genetic disorders to an unborn child. Once a pregnancy begins, prenatal testing is available to detect a number of disorders, as well.

Some genetic abnormalities, such as Down syndrome (a genetic abnormality that causes mental retardation, short stature, and flattened features), increase with the parents' ages. Women over 35 are at higher risk of having a child with Down syndrome—about 1 in 100 for a 40-year-old, compared to 1 in 10,000 for a 20-year-old mother or 3 in 1,000 for a 35-year-old mother. And it's not always just the mother's age that matters. An estimated 25 percent of Down syndrome cases can be attributed to increased age of the father.

Finally, it's important to remember that for most healthy women, the incidence of birth defects is very low—less than 3 percent. And of malformations that do occur, the most common are also the most treatable. Cleft palate and club foot, two of the more common birth defects, can be surgically repaired. Many heart malformations can be repaired with surgery so that children live normal lives.

For the most part, health experts say, a woman can do a lot to ensure the health of her child by maintaining a healthy lifestyle. ■

Rebecca D. Williams is a writer in Oak Ridge, Tenn.

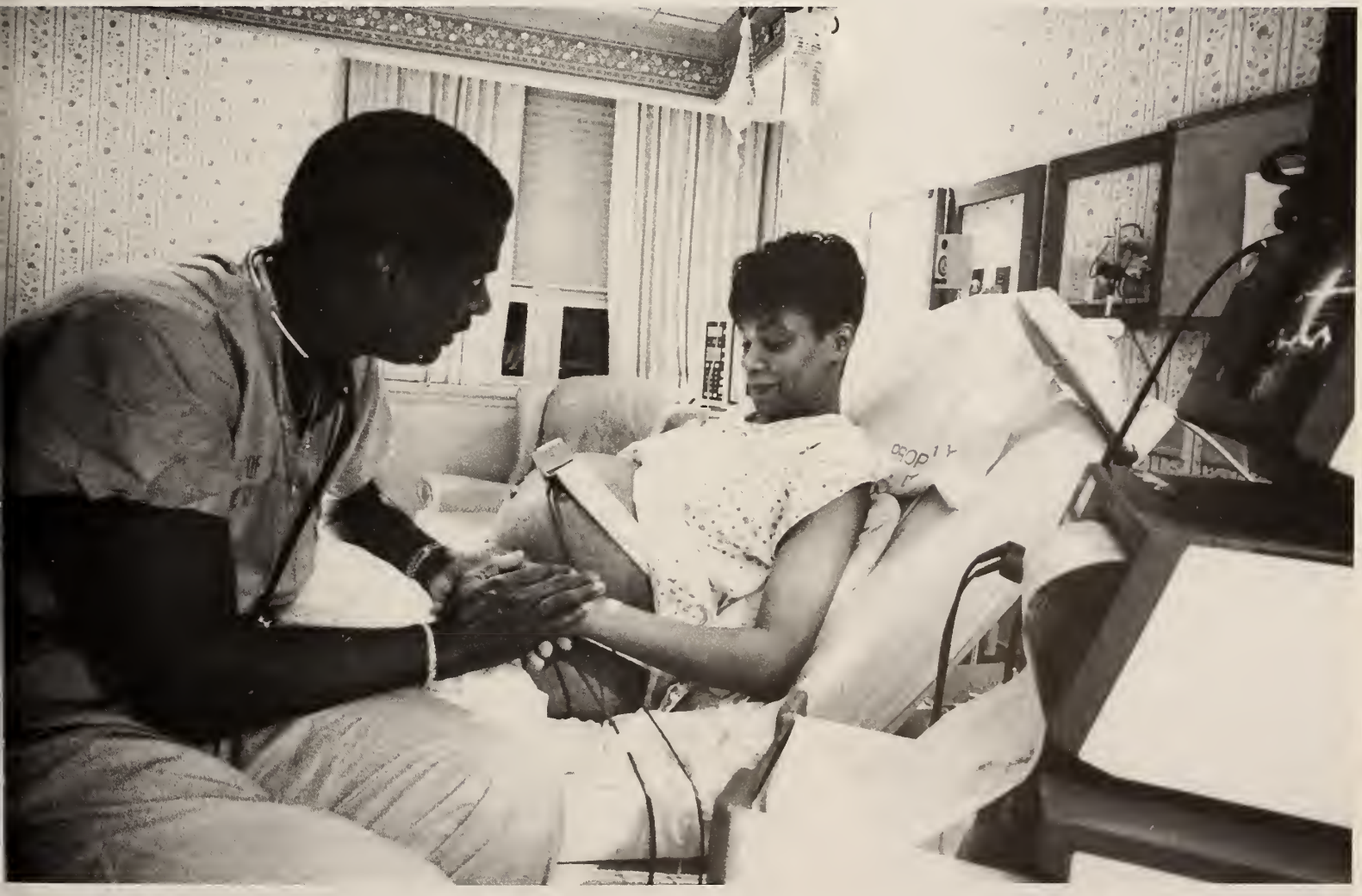
Medication and Labor

Birthing Babies in the '90s

by Isadora Stehlin

Almost every pregnant woman wonders how her labor is going to be. Will it be long and difficult? Will it be so short she'll barely make it to the hospital? And what about the pain?

"There are some women who come in and they're 9 centimeters dilated [dilation is complete at 10 centimeters, when the baby is usually ready to come out], and they say, 'I'm not really sure if I'm in labor,' " says Marion McCartney, a certified nurse-midwife in Bethesda, Md.



Phill Price, M.D., helps Vanessa Jones prepare for a contraction in Providence Hospital in Washington, D.C. After 14 hours of labor, Jones gave birth to a healthy girl through a normal vaginal delivery. Price, an obstetrician/gynecologist, also reviews drugs for FDA.

PHOTOGRAPH BY LAWRENCE RUGGERI

If the analgesics don't provide enough relief, epidurals may be the next step.

No pain; just a little discomfort and then the baby slides out. Wouldn't that be great?

McCartney says it happens. She also says that there are some women who, from the beginning, are in terrible agony. "Those are the extremes," says McCartney. "All the rest of us sort of fall in the middle. You can deal with the early part of labor and you can deal with the middle part of labor and then from 7 to 10 centimeters it really is terrible."

How does a woman deal with the terrible part? For a low-risk woman—one without any medical problems such as diabetes or high blood pressure—the way she copes frequently depends on the philosophy of the person giving her medical care.

Pain, Pain Go Away

Should a woman in labor receive painkillers and anesthetics? While some natural childbirth proponents believe that women who are knowledgeable about and well-prepared for labor will be able to handle the pain without drugs, some medical professionals can't imagine why any woman would want to deal with "unnecessary" pain.

Yet there is a middle ground.

"Labor and delivery should not be an ego trip," says Phill Price, M.D. "It's not about how much pain a woman can endure. It is about producing a healthy baby with a happy mother who is not traumatized for the rest of her life."

That said, Price, who has a private obstetrics practice in Washington, D.C., and reviews new drug applications for the Food and Drug Administration, is quick to point out that drugs are *not* the only answer. First he encourages his patients experiencing labor pains to walk and to breathe in patterns learned in prepared childbirth classes. At the hospital where he delivers babies, there's even a Jacuzzi whirlpool bath that some women find eases the pain.

"The key to having a baby is the ability to relax between the pains," he says. "If you can do it with breathing, fine. If you can do it with a Jacuzzi, fine. But it's easier said than done."

He explains that while many women may think they're relaxing between contractions, "they're actually waiting for that next pain to come. With drugs, a woman may actually go to sleep during the minute or two between contractions."

The drugs that can reduce the pain are either narcotics such as Demerol (meperidine) or non-narcotics such as Nubain (nalbuphine). The drugs should be administered only when a woman is between 3 and 8 centimeters dilated.

"The timing is most important," he says. The drugs may cause breathing problems for the baby if it is born with the drug in its system. Demerol should not be given within two hours of birth and Nubain not within one hour.

Epidural: A Double-Edged Sword

If the analgesics don't provide enough relief, epidurals may be the next step. Epidurals are anesthetic drugs that cause a loss of pain sensation in the lower half of the body by blocking the pain messages the nerves around the spine normally send to the brain. Injected into the lower back, the amount of numbness depends on the amount of the drug used.

Because administration of an epidural requires the skills of an anesthesiologist, nurse-midwives who, like McCartney, deliver at birth centers instead of hospitals must transfer their patients to a hospital if an epidural is necessary.

Anesthesiologist Murray Malin, M.D., who practices at the Columbia Hospital for Women in Washington, D.C., feels the benefits of epidurals far outweigh the risks, especially if the medication is given continuously through a pump. Administration through a pump has become more common in the last decade, as it allows a much lower concentration of the drug than would be necessary if the drug were given in intermittent doses.

When a pump isn't used, a higher dose of the drug becomes necessary to ensure enough pain relief as the medication's effects wear off, and this could result in a drop in the mother's blood pressure. That, in turn, could cause fetal distress. While those risks aren't eliminated with the use of a pump, they are substantially reduced. However, other risks still exist.

"Epidurals are a double-edged sword," says Price. "They help to relieve pain. They also have a tendency to arrest labor. Worst of all, epidurals take away the bearing down reflex [necessary to push the baby out]."

Those disadvantages—slowing the labor and not being able to push—outweigh the benefits, according to McCartney.

If labor slows down, the woman may be given Pitocin (oxytocin), a synthetic hormone, to speed things up. But contractions resulting from Pitocin are usually stronger than naturally occurring ones and may cause some fetal distress.

"The safest way to have babies is not to have any medication," she says. "Only if there is a problem—a terribly long labor, the woman is exhausted—should you start to intervene. You shouldn't intervene in a process that's going very well. Save those good anesthesias for people that really, really need them."

Forceps Controversial

A forceps is a surgical instrument that looks like two large spoons or salad tongs. A medical device, it is regulated by FDA. The doctor inserts the forceps into the birth canal, places the "spoons" around the baby's head, and, with each contraction, moves the baby down, and eventually out of, the birth canal.

Another medical device, the vacuum extractor, may be used in place of forceps. The extractor consists of a soft plastic or rubber cap held in place on the baby's head by suction from a vacuum pump.

Medical reasons for forceps delivery include a slow or irregular fetal heartbeat, failure of the baby's head to rotate into the proper position, or failure of the mother to push because of fatigue or an epidural.

Outlet forceps delivery—when the head is visible at the vaginal opening—involves the least risk. A study by Michael K. Yancey, M.D., and colleagues at the Madigan Army Medical Center, Tacoma, Wash., reported in the October 1991 issue of *Obstetrics and Gynecology,* found that an outlet forceps delivery in an uncomplicated labor causes no immediate harm to the baby. (The study did not address the possibility of any long-term effects.) However, the study did find these mothers had increased incidence of cuts and tears in the perineum (the area between the anus and the vagina) compared with women whose babies were delivered without forceps.

The risk level of outlet forceps delivery increases as the doctor moves the forceps higher into the birth canal.

"Difficult forceps deliveries involving a lot of rotation of the baby's head or pulling it down from high up in the birth

The risk level of outlet forceps delivery increases as the doctor moves the forceps higher into the birth canal.

Baby's Heartbeat a Harbinger

The unborn baby's heart rate is an important indicator of how things are going. The heartbeat can be monitored by a caregiver with a special stethoscope called a fetoscope or by an electronic fetal monitor.

Electronic fetal monitors, which are FDA-approved medical devices, measure the baby's heart rate continuously in one of two ways: externally or internally. With external monitors, two belts are placed around the mother's abdomen. One belt uses ultrasound to monitor the baby's heartbeat while the other measures the length of contractions. Internal monitors measure the baby's heart rate through an electrode attached to the baby's scalp.

Both types of monitors usually require the mother to stay in bed so the belts or electrodes stay in place.

Although measuring and recording every heartbeat sounds ideal, not everyone thinks the technology is an advantage.

"When I started delivering babies in 1971," says FDA's Phill Price, M.D., "physicians really believed that electronic fetal monitoring would be a tool that would tell us if a baby was going to be in trouble. But the last 5 to 10 years have told us that electronic fetal monitoring has not done a lot to actually improve the overall care of mothers or babies."

The theory behind the continuous monitoring is that the caregiver could note a change in the baby's heart rate immediately and take immediate action to prevent any harm to the baby. That action, almost always, is a Caesarean section.

The harm doctors are most concerned about is oxygen starvation, which can lead to conditions such as cerebral palsy.

However, in the last 25 years the incidence of cerebral palsy has remained the same—3 per 1,000—whether the patient was monitored or not, says Price.

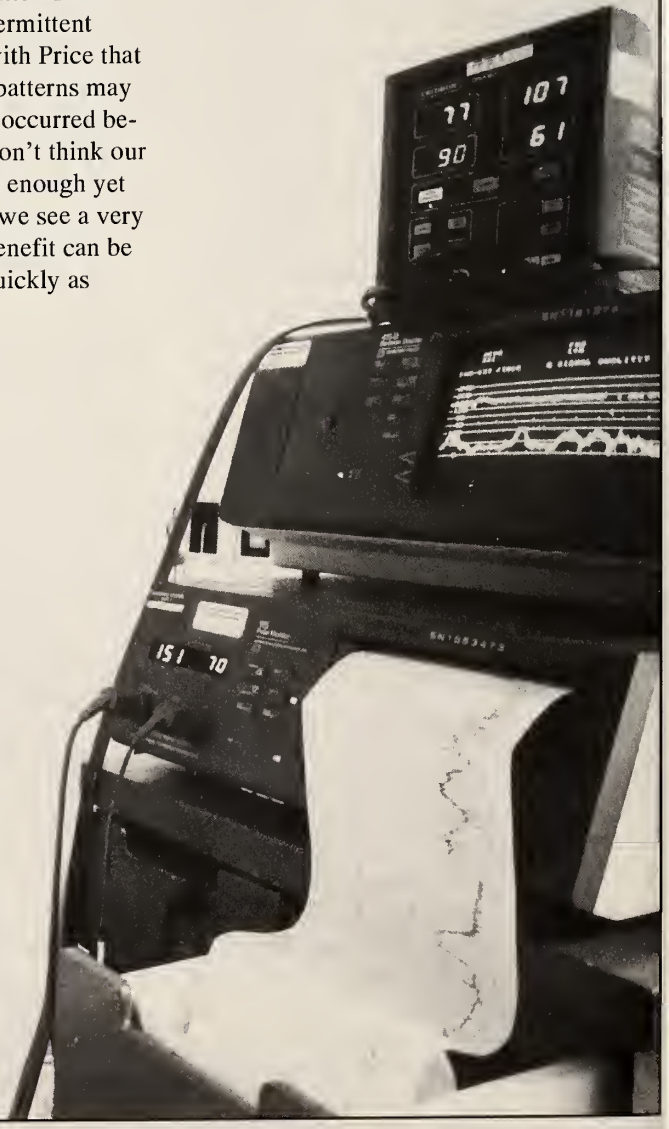
Some babies are going to have problems, and in all likelihood those problems occurred during the nine months of pregnancy, he explains. "To think that because I waited 5 or 10 or 15 minutes before doing a C-section the baby will come up with cerebral palsy is ludicrous," he says. "If you have a nurse who listens every 15 minutes in the first stage of labor and every five minutes in the second stage, you can get the same outcome."

"If I'm physically present, I can be pretty sure if things are fine or if things are starting to go wrong," says Barbara Good, a certified nurse-midwife in Takoma Park, Md.

But Wayne Cohen, M.D., of the Albert Einstein College of Medicine in New York City, says he has serious doubts about replacing electronic monitors with "old-fashioned" intermittent listening to the heart rate, because a monitor can pick up very uncommon patterns that might be missed by the intermittent method. While he agrees with Price that some of those uncommon patterns may indicate brain damage that occurred before labor even began, "I don't think our knowledge is sophisticated enough yet to be able to be sure when we see a very abnormal pattern that no benefit can be accrued by delivering as quickly as possible." ■

—I.S.

On the electronic fetal monitor (bottom and middle instruments), a printout gives continuous readings for the baby's heart rate and the mother's contractions. (The screen displays the same readings.) The numbers to the left of the printout are the heart rate (151) and strength of contraction (70). The box on top of the monitor indicates the mother's mean arterial pressure (77), pulse (90), and blood pressure (107/61).



canal are done quite infrequently in most parts of this country," says Wayne R. Cohen, M.D., vice chairman of the department of obstetrics and gynecology at the Albert Einstein College of Medicine in New York City. "The basic principle is that the more difficult the forceps delivery, the greater the risk."

The risks from a difficult forceps delivery range from minor injuries to the baby's head, such as bruises and indentations—both temporary—to serious problems, including skull fracture, eye injury, facial paralysis, and brain damage. Forceps may also cause damage to the mother's bladder or urethra (the tube that carries urine from the bladder to the outside of the body).

If the baby must be delivered right away, says Cohen, a Caesarean section (surgical delivery of the baby through an incision in the abdominal and uterine walls) involves less risk to both mother and baby and is therefore usually preferable to a difficult forceps delivery.

Besides helping a baby in distress, another reason for using forceps often cited by obstetricians is to shorten the second stage of labor and, in turn, reduce the risk of damage to the pelvic floor and tissues supporting the bladder and rectum that might occur with prolonged pushing. (The second stage of labor begins when the cervix is fully dilated and ends with the baby's birth. It can last for more than two hours, especially during a first labor.) But according to Yancey's study, routine use of forceps "does not significantly shorten the second stage of labor."

"No one wants to put forceps on babies unless there's a medical reason for doing it," says Price. That's why he tells his patients that he will let the epidural wear off so they can feel and push the baby out themselves.

McCartney advocates that women be allowed to keep pushing as long as fetal heart tones are good and progress is being made.

Cohen agrees. "Intervening with forceps during the second stage offers no advantage to the fetus as long as the fetal condition is good."

Cut or Tear?

Another intervention, one of the most common surgical procedures performed in North America, is episiotomy, the cutting of the perineum. The rationale behind routine episiotomy—that cutting is safer for the mother than the tearing that sometimes occurs during delivery—has been increasingly questioned in recent years.

The two types of episiotomies are:

- *Midline*—cut straight down from the vagina in the direction of the rectum. Considered to be more comfortable afterward and easier to repair.
- *Mediolateral*—perineum is cut diagonally to one side. Will prevent a tear from continuing on to the rectum, but is more difficult to repair and takes longer to heal than midline.

The American College of Obstetricians and Gynecologists recommends that doctors perform episiotomies if the baby is large, the woman's perineum is short, or to make room for a forceps delivery.

In addition, while an episiotomy can speed delivery by only a few minutes, even that amount of time can be critical if the baby is in distress.

But what about performing episiotomy just as a measure to prevent tearing?

The common philosophy is that a straight cut will be less painful and heal quicker than a jagged tear. But in one study in the July 1, 1992, *Online Journal of Current Clinical Trials,* there was no difference in pain levels or recovery time between women who had an episiotomy and women who had spontaneous tissue tears.

Even without the severe tear, any woman who gets an episiotomy gets a second-degree laceration, which means underlying tissue is involved. (Third-degree lacerations extend to the rectal sphincter (muscle) and fourth-degree go into the rectum.)

However, many women don't tear at all while giving birth or only tear the skin (first-degree laceration). First-degree tears may not require any stitches.

Another argument often cited to support performing episiotomies is that without the incision, the pressure on both the perineum and the baby's head could cause long-term damage to the mother's pelvic floor or to the baby's brain.

There are no strong studies to support or refute that hypothesis, according to Stephen B. Thacker, M.D., a researcher with the national Centers for Disease Control and Prevention.

Preventing tears is possible in some cases, but it requires extra effort from both the mother and the person delivering the baby.

Delivery position is one important factor in preventing tears. McCartney recommends upright positions such as sitting, squatting or kneeling because in these positions "the pelvic area, including the perineum, is relaxed, and pushing with gravity is easier."

Finally, the caregiver needs to encourage the mother not to push the baby out too fast. McCartney always tells her mothers, "I want you to push this baby out one hair at a time so you don't tear."

The Personal Touch

Perhaps the most important thing to remember is that one 'normal' labor may be very different from the next, says Price. "Things should be individualized," he says. "All deliveries are not the same."

Barbara Good, a certified nurse-midwife who delivers babies at the Columbia Hospital for Women, agrees. "Women are very individual in their responses to pain," she says. "If a woman says, 'I've had it and I'm really ready for [an epidural],' I'm not going to say no. I share the information and I let her choose. It's her birth. I want her to be happy with the experience." ■

Isadora Stehlin is a member of FDA's public affairs staff.

Breast Milk or Formula
Making the Right Choice for Your Baby

by Rebecca D. Williams and Isadora Stehlin

New parents want to give their babies the very best. When it comes to nutrition, the best first food for babies is breast milk.

More than two decades of research have established that breast milk is perfectly suited to nourish infants and protect them from illness. Breast-fed infants have lower rates of hospital admissions, ear infections, diarrhea, rashes, allergies, and other medical problems than bottle-fed babies.

Human milk contains at least 100 ingredients not found in formula.

"There are 4,000 species of mammals, and they all make a different milk. Human milk is made for human infants, and it meets all their specific nutrient needs," says Ruth Lawrence, M.D., professor of pediatrics and obstetrics at the University of Rochester School of Medicine in Rochester, N.Y., and spokeswoman for the American Academy of Pediatrics.

Health experts say increased breast-feeding rates would save consumers money, spent both on infant formula and in health-care dollars. It could save lives as well.

"We've known for years that the death rates in Third World countries are lower among breast-fed babies," says Lawrence. "Breast-fed babies are healthier and have fewer infections than formula-fed babies."

Although breast-feeding is still the best nourishment for infants, infant formula is a close enough second that babies not only survive but thrive.

Commercially prepared formulas are regulated by the Food and Drug Administration.

The safety of commercially prepared formula is also ensured by the agency's nutrient requirements and by strict quality control procedures that require manufacturers to analyze each batch of formula for required nutrients, to test samples for stability during the shelf life of the product, to code containers to identify the batch, and to make all records available to FDA investigators.

The composition of infant formula is similar to breast milk, but it isn't a perfect match, because the exact chemical makeup of breast milk is still unknown.

Human milk is very complex, and scientists are still trying to unravel and understand what makes it such a good source of nutrition for rapidly growing and developing infants. However, John C. Wallingford, Ph.D., an infant nutrition specialist with FDA's Center for Food Safety and Applied Nutrition, notes that "infant formula is increasingly close to breast milk."

More than half the calories in breast milk come from fat, and the same is true for today's infant formulas. This may be alarming to many American adults watching their intake of fat and cholesterol, especially when sources of saturated fats, such as coconut oil, are used in formulas. (In adults, high intakes of saturated fats tend to increase blood cholesterol levels more than other fats or oils.) But the low-fat diet recommended for adults doesn't apply to infants.

"Infants have a very high energy requirement, and they have a restricted volume of food that they can digest," says Wallingford. "The only way to get the energy density of a food up is to have a high amount of fat."

While greater knowledge about human milk has helped scientists improve infant formula, it has become "increasingly apparent that infant formula can never duplicate human milk," write John D. Benson, Ph.D, and Mark L. Masor, Ph.D., in the March 1994 issue of *Endocrine Regulations.* "Human milk contains living cells, hormones, active enzymes, immunoglobulins and compounds with unique structures that cannot be replicated in infant formula."

Benson and Masor, both of whom are pediatric nutrition researchers at infant formula manufacturer Abbott Laboratories, believe creating formula that duplicates human milk is impossible. "A better goal is to match the performance of the breastfed infant," they write. Performance is measured by the infant's growth, absorption of nutrients, gastrointestinal tolerance, and reactions in blood.

Wallingford agrees, explaining that while FDA's regulations on what goes into infant formula are to ensure there are enough nutrients, "that's just a starting point. What's really important is how infants thrive."

Human Milk for Human Infants

The primary benefit of breast milk is nutritional. Human milk contains just the right amount of fatty acids, lactose, water, and amino acids for human digestion, brain development, and growth.

Cow's milk contains a different type of protein than breast milk. This is good for calves, but human infants can have difficulty digesting it. Bottle-fed infants tend to be fatter than breast-fed infants, but not necessarily healthier.

Breast-fed babies have fewer illnesses because human milk transfers to the infant a mother's antibodies to disease. About 80 percent of the cells in breast milk are macrophages, cells that kill bacteria, fungi and viruses. Breast-fed babies are protected, in varying degrees, from a number of illnesses, including pneumonia, botulism, bronchitis, staphylococcal infections, influenza, ear infections, and German measles. Furthermore, mothers produce antibodies to whatever disease is present in their environment, making their milk custom-designed to fight the diseases their babies are exposed to as well.

A breast-fed baby's digestive tract contains large amounts of *Lactobacillus bifidus,* beneficial bacteria that prevent the growth of harmful organisms. Human milk straight from the breast is always sterile, never contaminated by polluted water or dirty bottles, which can also lead to diarrhea in the infant.

Human milk contains at least 100 ingredients not found in formula. No babies are allergic to their mother's milk, although they may have a reaction to something the mother eats. If she eliminates it from her diet, the problem resolves itself.

Sucking at the breast promotes good jaw development as well. It's harder work to get milk out of a breast than a bottle, and the exercise strengthens the jaws and encourages the growth of straight, healthy teeth. The baby at the breast also can control the flow of milk by sucking and stopping. With a bottle, the baby must constantly suck or react to the pressure of the nipple placed in the mouth.

Nursing may have psychological benefits for the infant as well, creating an early attachment between mother and child. At birth, infants see only 12 to 15 inches, the distance between a nursing baby and its mother's face. Studies have found that infants as young as 1 week prefer the smell of their own mother's milk. When nursing pads soaked with

breast milk are placed in their cribs, they turn their faces toward the one that smells familiar.

Many psychologists believe the nursing baby enjoys a sense of security from the warmth and presence of the mother, especially when there is skin-to-skin contact during feeding. Parents of bottle-fed babies may be tempted to prop bottles in the baby's mouth, with no human contact during feeding. But a nursing mother must cuddle her infant closely many times during the day. Nursing becomes more than a way to feed a baby; it's a source of warmth and comfort.

Benefits to Mothers

Breast-feeding is good for new mothers as well as for their babies. There are no bottles to sterilize and no formula to buy, measure and mix. It may be easier for a nursing mother to lose the pounds of pregnancy as well, since nursing uses up extra calories. Lactation also stimulates the uterus to contract back to its original size.

A nursing mother is forced to get needed rest. She must sit down, put her feet up, and relax every few hours to nurse. Nursing at night is easy as well. No one has to stumble to the refrigerator for a bottle and warm it while the baby cries. If she's lying down, a mother can doze while she nurses.

Nursing is also nature's contraceptive—although not a very reliable one. Frequent nursing suppresses ovulation, making it less likely for a nursing mother to menstruate, ovulate, or get pregnant. There are no guarantees, however. Mothers who don't want more children right away should use contraception even while nursing. Women who are breast-feeding can use barrier methods of birth control, such as condoms and diaphragms. Hormone-containing methods are not first choice. These include injections (such as Depo-Provera), implants (such as Norplant), and birth control pills. A woman who breast-feeds should consult her doctor about which type of contraception is appropriate for her until the baby is weaned.

Breast-feeding is economical also.

Tips for Breast-Feeding Success

It's helpful for a woman who wants to breast-feed to learn as much about it as possible before delivery, while she is not exhausted from caring for an infant around-the-clock. The following tips can help foster successful nursing:

- *Get an early start:* Nursing should begin within an hour after delivery if possible, when the infant is awake and the sucking instinct is strong. Even though the mother won't be producing milk yet, her breasts contain colostrum, a thin fluid that contains antibodies to disease.
- *Proper positioning:* The baby's mouth should be wide open, with the nipple as far back into his or her mouth as possible. This minimizes soreness for the mother. A nurse, midwife, or other knowledgeable person can help her find a comfortable nursing position.
- *Nurse on demand:* Newborns need to nurse frequently, at least every two hours, and not on any strict schedule. This will stimulate the mother's breasts to produce plenty of milk. Later, the baby can settle into a more predictable routine. But because breast milk is more easily digested than formula, breast-fed babies often eat more frequently than bottle-fed babies.
- *No supplements:* Nursing babies don't need sugar water or formula supplements. These may interfere with their appetite for nursing, which can lead to a diminished milk supply. The more the baby nurses, the more milk the mother will produce.
- *Delay artificial nipples:* It's best to wait a week or two before introducing a pacifier, so that the baby doesn't get confused. Artificial nipples require a different sucking action than real ones. Sucking at a bottle could also confuse some babies in the early days. They, too, are learning how to breast-feed.
- *Air dry:* In the early postpartum period or until her nipples toughen, the mother should air dry them after each nursing to prevent them from cracking, which can lead to infection. If her nipples do crack, the mother can coat them with breast milk or other natural moisturizers to help them heal. Vitamin E oil and lanolin are commonly used, although some babies may have allergic reactions to them. Proper positioning at the breast can help prevent sore nipples. If the mother's very sore, the baby may not have the nipple far enough back in his or her mouth.
- *Watch for infection:* Symptoms of breast infection include fever and painful lumps and redness in the breast. These require immediate medical attention.
- *Expect engorgement:* A new mother usually produces lots of milk, making her breasts big, hard and painful for a few days. To relieve this engorgement, she should feed the baby frequently and on demand until her body adjusts and produces only what the baby needs. In the meantime, the mother can take over-the-counter pain relievers, apply warm, wet compresses to her breasts, and take warm baths to relieve the pain.
- *Eat right, get rest:* To produce plenty of good milk, the nursing mother needs a balanced diet that includes 500 extra calories a day and six to eight glasses of fluid. She should also rest as much as possible to prevent breast infections, which are aggravated by fatigue. ■

—R.D.W.

Even though a nursing mother works up a big appetite and consumes extra calories, the extra food for her is less expensive than buying formula for the baby. Nursing saves money while providing the best nourishment possible.

When Formula Is Necessary

There are very few medical reasons why a mother shouldn't breast-feed, according to Lawrence.

Most common illnesses, such as colds, flu, skin infections, or diarrhea, cannot be passed through breast milk. In fact, if a mother has an illness, her breast milk will contain antibodies to it that will help protect her baby from those same illnesses.

A few viruses can pass through breast milk, however. HIV, the virus that causes AIDS, is one of them. Women who are HIV positive should not breast-feed.

A few other illnesses—such as herpes, hepatitis, and beta streptococcus infections—can also be transmitted through breast milk. But that doesn't always mean a mother with those diseases shouldn't breast-feed, Lawrence says.

"Each case must be evaluated on an individual basis with the woman's doctor," she says.

Breast cancer is not passed through breast milk. Women who have had breast cancer can usually breast-feed from the unaffected breast. Studies have shown, however, that breast-feeding a child reduces a woman's chance of developing breast cancer later.

Silicone breast implants usually do not interfere with a woman's ability to nurse, but if the implants leak, there is some concern that the silicone may harm the baby. Some small studies have suggested a link between breast-feeding with implants and later development of problems with the child's esophagus. Further studies are needed in this area. But if a woman with implants wants to breast-feed, she should first discuss the potential benefits and risks with her child's doctor.

Tough but Worthwhile

For all its health benefits, breast-feeding isn't always easy. In the early weeks, it can be painful. A woman's nipples may become sore or cracked. She may experience engorgement more than a bottle-feeding mother, when the breasts become so full of milk they're hard and painful. Some nursing women also develop clogged milk ducts, which can lead to mastitis, a painful infection of the breast. While most nursing problems can be solved with home remedies, mastitis requires prompt medical care (see "Tips for Breast-Feeding Success").

Women who plan to go back to work soon after birth will have to plan carefully if they want to breast-feed. If her job allows, a new mother can pump her breast milk several times during the day and refrigerate or freeze it for the baby to take in a bottle later. Some women alternate nursing at night and on weekends with daytime bottles of formula.

In either case, a nursing mother is physically tied to her baby more than a bottle-feeding mother. The baby needs her for nourishment, and she needs to nurse regularly to avoid getting uncomfortably full breasts. But instead of feeling it's a chore, nursing mothers often cite this close relationship as one of the greatest joys of nursing.

If a woman is unsure whether she wants to nurse, she can try it for a few weeks and switch if she doesn't like it. It's very difficult to switch to breast-feeding after bottle-feeding is begun.

If she plans to breast-feed, a new mother should learn as much as possible about it before the baby is born. Obstetricians, pediatricians, childbirth instructors, nurses, and midwives can all offer information about nursing. But perhaps the best ongoing support for a nursing mother is someone who has successfully nursed a baby.

La Leche League, an international support organization for nursing mothers, has chapters in many cities that meet regularly to discuss breast-feeding problems and offer support.

Most La Leche League chapters will allow women to come to a few meetings without charge. League leaders offer advice by phone as well. To find a convenient La Leche League chapter, call

Medicines And Nursing Mothers

Most medications have not been tested in nursing women, so no one knows exactly how a given drug will affect a breast-fed child. Since very few problems have been reported, however, most over-the-counter and prescription drugs, taken in moderation and only when necessary, are considered safe.

Even mothers who must take daily medication for conditions such as epilepsy, diabetes, or high blood pressure can usually breast-feed. They should first check with the child's pediatrician, however. To minimize the baby's exposure, the mother can take the drug just after nursing or before the child sleeps. In the January 1994 issue of *Pediatrics*, the American Academy of Pediatrics included the following in a list of drugs that are usually compatible with breast-feeding:

- acetaminophen
- many antibiotics
- anti-epileptics (although one, Primidone, should be given with caution)
- most antihistamines
- alcohol in moderation (large amounts of alcohol can cause drowsiness, weakness, and abnormal weight gain in an infant)
- most antihypertensives
- aspirin (should be used with caution)
- caffeine (moderate amounts in drinks or food)
- codeine
- decongestants
- ibuprofen
- insulin
- quinine
- thyroid medications

Drugs That Are NOT Safe While Nursing

Some drugs can be taken by a nursing mother if she stops breast-feeding for a few days or weeks. She can pump her milk and discard it during this time to keep up her supply, while the baby drinks previously frozen milk or formula.

Radioactive drugs used for some diagnostic tests like Gallium-69, Iodine-125, Iodine-131, or Technetium-99m can be taken if the woman stops nursing temporarily.

Drugs that should never be taken while breast-feeding include:

Image provided by © 1994 PhotoDisk Inc.

Bromocriptine (Parlodel): A drug for Parkinson's disease, it also decreases a woman's milk supply.

Most Chemotherapy Drugs for Cancer: Since they kill cells in the mother's body, they may harm the baby as well.

Ergotamine (for migraine headaches): Causes vomiting, diarrhea, convulsions in infants.

Lithium (for manic-depressive illness): Excreted in human milk.

Methotrexate (for arthritis): Can suppress the baby's immune system.

Drugs of Abuse: Some drugs, such as cocaine and PCP, can intoxicate the baby. Others, such as amphetamines, heroin and marijuana, can cause a variety of symptoms, including irritability, poor sleeping patterns, tremors, and vomiting. Babies become addicted to these drugs.

Tobacco Smoke: Nursing mothers should avoid smoking. Nicotine can cause vomiting, diarrhea and restlessness for the baby, as well as decreased milk production for the mother. Maternal smoking or passive smoke may increase the risk of sudden infant death syndrome and may increase respiratory and ear infections. ■

(1-800) LA-LECHE or contact the organization's world wide web site at *http://www.lalecheleague.org/.*

Formula Choices

If the mother cannot or chooses not to breast-feed, normal, full-term infants should get a conventional cow's-milk-based formula, according to John N. Udall Jr., M.D., chief of nutrition and gastroenterology at Children's Hospital of New Orleans. However, adverse reactions to the protein in cow's milk formula or symptoms of lactose intolerance (lactose is the carbohydrate in cow's milk) may require switching to another type of formula, he says.

Symptoms that may indicate an adverse reaction to cow's milk protein include vomiting, diarrhea, abdominal pain, and rash. With lactose intolerance, the most common symptoms are excessive gas, abdominal distension and pain, and diarrhea. Since some of the symptoms overlap, a stool test may be necessary to determine the culprit. Usually, lactose intolerance will produce acidic stools that contain glucose. If the protein is the problem, stools will be nonacidic and have flecks of blood.

The main alternative to cow's milk formula is soy formula.

The carbohydrates in most soy formulas are sucrose and corn syrup, which are easily digested and absorbed by infants. However, soy is not as good a protein source as cow's milk. Also, babies don't absorb some minerals, such as calcium, as efficiently from soy formulas. Therefore, according to the American Academy of Pediatrics, "Healthy full-term infants should be given soy formula only when medically necessary."

For a child who can't tolerate cow's milk protein, William J. Klish, M.D., chairman of the American Academy of Pediatrics Committee on Nutrition recommends the use of hydrolyzed-protein formula. Although hydrolyzed-protein formulas are made from cow's milk, the protein has been broken up into its component parts. Essentially, it's been predigested, which decreases the likelihood of an allergic reaction.

Whole Milk for First Birthday

The American Academy of Pediatrics recommends that babies be breast-fed for six to 12 months. The only acceptable alternative to breast milk is infant formula. Solid foods can be introduced when the baby is 4 to 6 months old, but a baby should drink breast milk or formula, not regular cow's milk, for a full year.

"There aren't any rules about when to stop breast-feeding," says Ruth Lawrence, M.D., professor of pediatrics and obstetrics at the University of Rochester School of Medicine in Rochester, N.Y., and spokeswoman for the academy. "As long as the baby is eating age-appropriate solid foods, a mother may nurse a couple of years if she wishes. A baby needs breast milk for the first year of life, and then as long as desired after that." Formula, however, should not be continued after the first birthday. That's the time to introduce milk. For all babies the milk, however, should be whole milk. Low-fat and skim milk do not have enough fat and calories to supply the nutritional needs of a 1-year-old, explains John Udall, chief of nutrition and gastroenterology at Children's Hospital of New Orleans. At that age, "the child is growing so quickly, and the fat is so important for brain and central nervous system development," he says. "The recommendation that our daily intake of fat should compose less than 30 percent of our caloric intake does not apply to children under 2 years of age."

New on the market are special toddler formulas that claim to be better than milk. The formulas are good nutritionally, says Udall, but they're not necessary. "A well-balanced diet with milk and juices would be just as good in a healthy, normally active, normally growing child," says Udall.

William Klish, chairman of the American Academy of Pediatrics Committee on Nutrition, says that if a child needs to take a vitamin supplement, the toddler formula, fortified with a full range of vitamins and minerals, including iron, can serve that purpose. In addition, the toddler formulas don't need refrigeration, making them a convenient choice for snacks away from home. ■

—I.S.

PHOTOGRAPH BY NORMAN WATKINS

Iron

The infant formulas currently available in the United States are either "iron-fortified"—with approximately 12 milligrams of iron per liter—or "low iron"—with approximately 2 milligrams of iron per liter.

"There should not be a low-iron formula on the market for the average child because a low-iron formula is a nutritionally deficient formula," says Klish. "It doesn't provide enough iron to maintain proper blood cell counts or proper hemoglobin." (Hemoglobin is a blood protein that carries oxygen from the lungs to the tissues, and carbon dioxide from the tissues to the lungs.)

In addition, studies have shown that school children who had good iron status as infants because they were fed iron-fortified formula performed better on standardized developmental tests than children with poor iron status. However, Wallingford says that "FDA has permitted marketing of low-iron formulas because some pediatricians prefer to use them, with the caveat that the physician would be monitoring iron status and prescribing iron supplements when appropriate."

Why is there low-iron formula on the market? "In the past there have been a lot of symptoms that have been attributed to iron, including abdominal discomfort, constipation, diarrhea, colic, and irritability," says Klish. "Also there was some concern about too much iron interfering with the immune system. All of those concerns and questions have been laid to rest with appropriate studies."

Another reason for originally producing low-iron formulas was that human milk contains low amounts of iron—less than a milligram per liter. However, it is now understood that an infant absorbs virtually 100 percent of the iron from human milk, but considerably less from infant formula.

Cooking Lessons

Both milk and soy formulas are available in powder, liquid concentrate, or ready-to-feed forms. The choice should depend on whatever the parents find convenient and can afford.

Whatever form is chosen, proper preparation and refrigeration are essential. Opened cans of ready-to-feed and liquid concentrate must be refrigerated and used within the time specified on the can. Once the powder is mixed with water, it should also be refrigerated if it is not used right away. The exact amounts of water recommended on the label must be used. Under-diluted formula can cause problems for the infant's organs and digestive system. Over-diluted formula will not provide adequate nutrition, and the baby may fail to thrive and grow.

Until recently, the American Academy of Pediatrics felt that municipal water supplies were safe enough without boiling the water before mixing with the formula. But because of the contamination of Milwaukee's water with the parasite *Cryptosporidium* in 1993, "the whole business of boiling water has come up again," says Klish. "The academy is now again recommending boiling water for infant formulas."

Homemade formulas should not be used.

Klish advises heating the water until it reaches a rolling boil, continue to boil for one to two minutes, and then let it cool. "That should take care of all the bacteria and parasites that might be in the water," he explains.

The American Academy of Pediatrics does not have any recommendations about bottled water. Klish says bottled water is fine, but it still needs to be boiled. "There's no reason to think that bottled water is any safer than city water," he says.

Bottled water must meet specific FDA quality standards for contaminants. These are set in response to requirements that the Environmental Protection Agency has established for tap water.

A new regulation published in the Nov. 13, 1995, *Federal Register* sets standard definitions for different types of bottled waters, helping resolve possible confusion about what different terms mean.

The regulation also requires accurate labeling of bottled waters marketed for infants. If a product is labeled "sterile," it must be processed to meet FDA's requirements for commercial sterility. Otherwise, the labeling must indicate that it is not sterile and should be used as directed by a physician or according to infant formula preparation instructions.

What about sterilizing the bottles and nipples? "Dishwashers tend to sterilize bottles and nipples fairly well," says Klish. They can also be sterilized by placing them in a pan of boiling water for five minutes.

Warming the formula before feeding isn't necessary for proper nutrition, but most infants prefer the formula at least at room temperature. The best way to warm a bottle of formula is by placing the bottle in a pot of water and heating the pot on the stove.

Don't Try This at Home

Homemade formulas should not be used, says Nick Duy, a consumer safety officer in FDA's Office of Special Nutritionals. Homemade formulas based on cow's milk don't meet all of an infant's nutritional needs, and cow's milk protein that has not been cooked or processed is difficult for an infant to digest. In addition, the high protein and electrolyte (salt) content of cow's milk may put a strain on an infant's immature kidneys. Substituting evaporated milk for whole milk may make the homemade formula easier to digest because of the effect of processing on the protein, but the formula is still nutritionally inadequate and still may stress the kidneys.

Today's infant formula is a very controlled, high-tech product that can't be duplicated at home, says Udall. ■

Rebecca D. Williams is a writer in Oak Ridge, Tenn. Isadora Stehlin is a member of FDA's public affairs staff.

Understanding Cosmetics

More Complex Than at First Blush

by Judith E. Foulke and Isadora Stehlin

From blushers and lipsticks to moisturizers that claim to ease wrinkles, there's a vast array of cosmetics to choose from. In deciding whether to use these products, today's woman is concerned with their safety and about the truthfulness of cosmetic claims.

"Most cosmetics contain ingredients that are promoted with exaggerated claims of beauty or long-lasting effects to create an image," says John E. Bailey, Ph.D., director of the Food and Drug Administration's Office of

Though cosmetic advertising may swell with flowery description, when it comes to listing what's actually in the products, the words turn clinical.

Cosmetics and Colors. "Image is what the cosmetic industry sells through its products, and it's up to the consumer to believe it or not," Bailey says.

In the past, cosmetic manufacturers have depended upon mysterious "gimmick" additives, such as turtle oil to promote skin rejuvenation or tighten chin muscles, shark oil, queen bee royal jelly, chick embryo extract, horse blood serum, and pigskin extracts.

Promotion of these "gimmick" additives, combined with today's more sophisticated cosmetic ingredients, is what Bailey and the cosmetic industry call "puffery."

The argument is sometimes made that while Congress intended to safeguard the health and economic interests of consumers with the Federal Food, Drug, and Cosmetic Act, it also meant to protect a manufacturer's right to market a product free of excessive government regulation. And, in an industry that sells personal image, especially images of beauty and sex appeal, not allowing the puffery claims would certainly hurt the marketing, says Bailey.

Language of Chemistry

Though cosmetic advertising may swell with flowery description, when it comes to listing what's actually in the products, the words turn clinical. A quick glance at the back of the cosmetic label is all it takes to see that the ingredients are written in the language of chemistry. Chemical names are the only way ingredients can be listed because that's what they are. (See "Chemical Translations.")

Many ingredients are marketed with trade names, but these often provide little clue to the identity and intended use of the material. Trade names in the ingredient list could be confusing to consumers purchasing a cosmetic because they would have no way to compare similar ingredients in similar products. Also, some trade names include mixtures of raw materials—for example, an ingredient combined with a preservative. For this reason, manufacturers may not use trade names to declare cosmetic ingredients on product package labels, as required by the Federal Fair Packaging and Labeling Act of 1966.

Despite the highly technical language of the ingredient list, Bailey says it's entirely possible for consumers to get valuable information about a product by checking the label—front and back.

The law allows a manufacturer to ask FDA to grant "trade secret" status for a particular ingredient. FDA grants this status under very limited circumstances and after careful review of the manufacturer's data. The manufacturer must prove that the ingredient imparts some unique property to a product and that the ingredient is not well-known in the industry. If trade secret status is granted, the ingredient does not have to be listed on the label, but the list must end with the phrase "and other ingredients." Ingredients are listed in descending order, starting with the greatest amount in the product.

The International Cosmetic Ingredient Dictionary, published by the Cosmetic, Toiletry, and Fragrance Association, Inc., provides a comprehensive (but not exhaustive) list of the most widely known cosmetic ingredients and their definitions and trade names. However, manufacturers are not restricted to ingredients listed in this dictionary. With the exception of color additives and a few ingredients prohibited by regulation, a cosmetic manufacturer may, on its own responsibility, use any raw material as a cosmetic ingredient and market the product without FDA approval.

The dictionary, and all other compendia FDA recognizes to name ingredients, are available for reference at many public libraries, or at the Office of the Federal Register, 1100 L St., N.W., Washington, DC 20408.

Cosmetic ingredient declaration regulations apply only to products offered for sale to consumers. Products used exclusively by beauticians in beauty salons or cosmetic studios, as well as cosmetic samples such as those distributed free at hotels, are not subject to the ingredient labeling rules. They must, however, state the name and address of the manufacturer, packer or distributor, and must give an accurate statement of quantity and all necessary warning statements.

Other Baffling Names

In addition to the chemical names of ingredients, some other terms, mystifying to consumers, may appear on cosmetics labels. Here is what FDA knows about some of these terms:

• *Alpha hydroxy acids* are chemicals, some of which naturally occur in sour milk, sugarcane, and fruit, that are promoted to improve skin condition and smooth fine lines and wrinkles. A study sponsored by the cosmetics industry indicates that these products may make users more sensitive to sunlight and especially to the ultraviolet (UV) radiation component of sunlight. UV exposure can damage the skin and at high doses, especially over a long period, can cause skin cancer. In addition, as of January 1997, FDA had received about 100 reports of adverse effects with alpha hydroxy acid (AHA) products, ranging from mild irritation and stinging to blistering and burns.

If you usually have sensitive skin, test any product that contains an AHA on a small area of skin before applying it to a large area. It is wise to use a sunscreen before going into the sun, whether or not you use products with AHAs; the industry AHA study makes

A woman tries out eye shadow in a store by using disposable applicators and single-use samples.

If trade secret status is granted, the ingredient does not have to be listed on the label, but the list must end with the phrase "and other ingredients."

this precaution even more important.

If you use cosmetics with AHAs and experience skin irritation or prolonged stinging, stop using the product and consult your physician.

• *Liposomes* are microscopic sacs, or spheres, manufactured from a variety of natural or synthetic fatty substances. When properly mixed with water, these substances form spheres, which can "trap" any substance that will dissolve in water or oil.

Manufacturers say that liposomes act like a delivery system, and that, when present in a cream or lotion, liposomes can more easily penetrate the surface skin to underlying layers, "melt," and deposit other ingredients of the product in the lower skin layers.

• *Nayad* is a trade name for yeast extract. The manufacturer's literature describes Nayad as a "new system that takes yeast cells and refines them hundreds of times. ... What results is a highly concentrated, odor-free, unusually potent yeast extract ... ." The same literature reports that "no one really knows how Nayad is working in the skin; all we know for certain is the way it makes the skin look and feel. Test subjects report a noticeable smoothing of lines and wrinkles." FDA has no data to either substantiate or refute these claims.

• *Vitamins* are added to cosmetics by manufacturers because foods containing vitamins A, D, E, K, and some of the B complex group are necessary in diets to maintain healthy skin and hair. Using these vitamins in cosmetics implies that skin will be nourished by them.

But Stanley R. Milstein, Ph.D., special assistant to the director of FDA's Office of Cosmetics and Colors, says the notion that skin can be nourished by a vitamin applied to its surface has not been proven clinically. For that reason, says Milstein, a vitamin added to a cosmetic product must be listed in the ingredient label by its chemical name so that it doesn't convey a misleading message.

It is generally accepted that a sufficient quantity of vitamin E (shown on ingredient lists as tocopherol), an antioxidant, preserves the fatty components in cosmetic creams and lotions to prevent off-color and off-odors.

• *Aloe vera* is a plant from the lily family whose anti-irritant properties have been recognized since before the days of Cleopatra. But, Milstein explains, aloe vera is expensive because it requires delicate processing. A product that contains the 5 to 10 percent aloe vera necessary for the anti-irritant properties to be effective would send the price out of range for many consumers, so almost all products contain less.

What About Biological Ingredients?

A number of biological products in cosmetics have raised consumer concern:

• *Human placenta* is the nourishing lining of the womb (uterus), expelled after birth. Though manufacturers previously made tissue-growth and wrinkle-removing claims for placenta, they stopped after FDA pointed out these are medical claims. Today, placenta used in cosmetics is marketed as a source of protein. It is washed and processed many times to destroy any harmful bacteria or viruses. The products also include a wide variety

of substances, such as alcohol and preservatives, that present a hostile environment to any viruses or bacteria the placenta might have carried.

- *Amniotic liquid* (from cow or ox) is the fluid that surrounds the developing fetus and protects it from physical injury. It is promoted for benefits similar to those of human placenta and has limited use in moisturizers, hair lotions, scalp treatments, and shampoos.
- *Collagen* (from young cows) is the protein substance found in connective tissue. (Connective tissue binds together and supports organs and other body structures.) In cosmetics, collagen has a moisturizing effect. FDA says there is no convincing evidence that collagen can penetrate the skin and have an effect below the surface.
- *Cerebrosides* (from animals or plants) are a type of glycolipid (a chemically combined form of fatty substance and carbohydrate) produced naturally in the deepest layer of skin and secreted to the outside of the cells where, manufacturers claim, they serve as a protective coating to foster skin moisture and suppleness. FDA has not evaluated the studies on which these claims are based.

Cosmetics That Are Also Drugs

Cosmetics making therapeutic claims—that they may affect the structure or function of the body—are regulated as drugs and cosmetics and must meet the labeling requirements for both. One way you can tell if you're dealing with such a product is if the first entry in the ingredient list says "Active Ingredient." (The active ingredient is the chemical that makes the product effective, and it must be safe for its intended use.) Active ingredients must be listed first, followed by a list of all inactive cosmetic ingredients.

Examples of products that are both cosmetics and drugs are deodorants that also claim to stop perspiration, dandruff shampoos, fluoride toothpastes, and sunscreens and sun-blocking cosmetics (including foundations that contain sunscreens).

A product with a drug and cosmetic classification must be scientifically proven safe and effective for its therapeutic claims before it is marketed. If the product is not, FDA considers it to be a misbranded drug and can take regulatory action.

Preventing Problems

Cosmetic products that are not regulated both as drugs should be thoroughly tested for safety. But the law does not require manufacturers to submit safety testing data to the agency for review when such tests are carried out.

In cases where the substantiation of safety for a cosmetic product or any of its ingredients is inadequate or has not been carried out, FDA requires that the cosmetic bear the following conspicuous statement on the front of the package label: "Warning: The Safety of This Product Has Not Been Determined."

For example, all cosmetics in self-pressurized containers, such as shaving creams, must have specifically worded warnings against spraying near the eyes, puncturing, incinerating, storing, and intentionally misusing. "Keep out of the reach of children" is also required for all products in pressurized containers.

Those aerosol products containing halocarbon or hydrocarbon propellants must bear the exact wording: "Warning—Use only as directed. Intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal."

Other products requiring specific wording include:

• *Detergent bubble bath products*—may irritate skin and the urinary tract through excessive use or prolonged exposure. The labeling instructs users to discontinue the product if rash, redness or itching occur, to consult a physician if irritation persists, and to keep out of reach of children. In addition, for foaming detergent bubble bath products intended for use by children, the phrase "except under adult supervision" may be added.

• *Feminine deodorant sprays intended for use in the genital area*—are for external use only and should not be applied to broken, irritated or itching skin. A physician should be consulted if persistent, unusual odor or discharge occurs. The statement instructs users to discontinue immediately if rash, irritation or discomfort develops. Labeling on self-pressurized containers must state that the product should be sprayed at least 8 inches from the skin.

Cosmetic product labels must also bear warning statements whenever necessary or appropriate to prevent a health hazard that may be associated with the product.

The following products require explicit warnings, though not with specific wording:

• *Depilatories and hair straighteners*—are highly alkaline; if they are used incorrectly, they may cause serious skin irritation.

• *Shampoos, rinses and conditioners*—can cause eye problems that range from irritation to more extensive damage.

• *Nail builders* (elongators, extenders, hardeners, and enamels)—can cause irritation, inflammation and infection of the nail bed and nail fold (where the nail meets the finger). Nail hardeners and enamels often contain formaldehyde and formaldehyde-releasing preservatives, which may cause allergic reactions. In addition, these products should have a flammability caution statement because volatile flammable organic solvents are often used in their formulation. If the solvent acetonitrile is present, specific child-resistant packaging is required by law to minimize the potential of poisoning of young children.

• *Other flammable products* (such as aerosol hair sprays containing alcohol and an isobutane propellant)—also include caution statements about avoiding heat, fire and smoking during use until the product is fully dry.

In addition, under the coal-tar hair-dye exemption, coal-tar color-containing hair-dye products contain ingredients that may irritate the skin of certain individuals, and a preliminary test should first be made. Users are cautioned not to dye eyelashes or eyebrows, which could result in blindness. The ammonia, soaps, detergents, conditioning agents, and dyes in hair-dye products are all strong eye irritants and could also cause allergic reactions in other areas.

Manufacturers often use warning statements on labels when there is even a small chance of a problem. Baby products often contain such warnings. Baby powder, for example, if used carelessly and accidentally inhaled by the baby in large amounts, can block the infant's bronchial and lung passages and cause suffocation.

Even one report of an acute injury, usually caused by a contaminated product, results in quick action by the agency. "We'll inspect the establishment, talk to the consumer, talk to the doctor, collect samples, and analyze them to determine the extent of contamination," says Bailey.

Contaminated makeup is often the result of microbial contamination of raw materials, especially water and so-called "natural" raw materials. These can serve as a nutrient source for the bacterial growth. Other factors include inadequate preservation of the final cosmetic product and product misuse. Every time you open a bottle of foundation or case of eye shadow, microorganisms in the air have an opportunity to rush in. But adequately preserved products can kill off enough of the little bugs to keep the product safe.

Occasionally, however, a product will be seriously contaminated. According to

Beauty on the Safe Side

Here are some important precautions to help you protect yourself and the quality of your cosmetics:

• Never put make-up on while driving or while you are in a moving vehicle.

• Keep makeup containers tightly closed except when in use.

• Keep makeup out of sunlight; light can degrade preservatives, fragrance, and unsaturated lipid components.

• Don't use eye cosmetics if you have an eye infection, such as conjunctivitis, and throw away all products you were using when you first discovered the infection.

• Never add any liquid to bring the product back to its original consistency. Adding water or, even worse, saliva could introduce bacteria that could easily grow out of control or dilute the preservative to less than effective concentration.

• Never share.

• Throw makeup away if the color changes or an odor develops. ■

—I.S.

Taking extra care when putting on eye makeup will help avoid injuries.

Regulating Cosmetics

The Federal Food, Drug, and Cosmetic Act defines cosmetics as "articles other than soap which are applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance."

It is against the law to distribute cosmetics that contain poisonous or harmful substances that might injure users under normal conditions. Manufacturing or holding cosmetics under insanitary conditions, using nonpermitted colors, or including any filthy, putrid or decomposed substance are also illegal.

Except for color additives and a few prohibited ingredients, a cosmetic manufacturer may use any ingredient or raw material and market the final product without government approval. The prohibited ingredients are:

- biothionol
- hexachlorophene
- mercury compounds (except under certain conditions as preservatives in eye cosmetics)
- vinyl chloride and zirconium salts in aerosol products
- halogenated salicylanilides
- chloroform
- methylene chloride
- fully halogenated chlorofluorocarbon propellants

Manufacturers must test color additives for safety and gain FDA approval for their intended use.

Cosmetic firms may voluntarily register their manufacturing plants with FDA, file cosmetic formulas, and report adverse reactions. ■

—I.S.

FDA data, most cases of contamination are due to manufacturers using poorly designed, ineffective preservative systems and not testing the stability of the preservatives during the product's customary shelf life and under normal use conditions.

Testing the Testers

When using makeup, sharing is definitely taboo—whether you're at home, at work, or out shopping. Shared testers at department store cosmetic counters are even more likely to become contaminated than the same products in an individual's home, according to the 1989 FDA report.

"At home, the preservatives have time—usually a whole day—to kill the bacteria that is inevitably introduced after each use," says Bailey. "But in a store, there may be only minutes between each use. The preservatives can't handle it."

Today sterile, disposable swabs or cotton balls are available for use when testing products at many cosmetic counters. Be sure you use them—or request such sterile, disposable testers if they are not already placed on the counter.

Coping with Allergies

Fragrances are a common source of allergies in cosmetics, as are the moisturizer lanolin (a sheep wool extract) and preservatives.

People who have had allergic reactions to cosmetics may try hypoallergenic or allergy-tested products. These are, however, only a partial solution for some and no solution at all for others.

"Hypoallergenic can mean almost anything to anybody," says Bailey.

"Hypo" means "less than," and hypoallergenic means only that the manufacturer feels that the product is less likely than others to cause an allergic reaction. Although some manufacturers do clinical testing, others may simply omit perfumes or other common problem-causing ingredients. But there are no regulatory standards on what constitutes a hypoallergenic product.

Likewise, label claims that a product is "dermatologist-tested," "sensitivity tested," "allergy tested," or "nonirritating" carry no guarantee that it won't cause reactions.

Like hypoallergenic, "natural" can mean anything to anybody.

Chemical Translations

At present, the cosmetic industry selects from more than 5,000 different ingredients. Here are some common cosmetic ingredients:

Alpha Hydroxy Acids
- glycolic acid
- lactic acid
- malic acid
- citric acid
- hydroxycaprylic acid
- mixed, tri-alpha hydroxy, or triple fruit acids
- sugarcane extract
- glycomer in crosslinked fatty acids alpha nutrium (three AHAs)

Moisturizers
- cetyl alcohol (fatty alcohol)
- dimethicone
- isopropyl lanolate, myristate, or palmitate
- propylene glycol
- lanolin
- octyl dodecanol
- oleic acid (olive oil)
- panthenol (vitamin B-complex derivative)
- stearic acid and stearyl alcohol

Chelating Agents and Antioxidants
- trisodium and tetrasodium edetate (EDTA)
- tocopherol (vitamin E)
- ascorbic acid (vitamin C) and ascorbyl palmitate

Antimicrobial Preservatives
- butyl, propyl, ethyl, and methyl parabens
- DMDM hydantoin
- methylisothiazolinone and choromethylisothiazolinone
- phenoxyethanol (also rose ether fragrance component)
- quaternium-15

Thickeners and Waxes
(used in stick products such as lipsticks and blushers)
- candelilla, carnauba, and microcrystalline waxes
- carbomer and polyethylene

Solvents to Dilute
- butylene glycol and propylene glycol
- cyclomethicone
- ethanol (alcohol)
- glycerin

Emulsifiers to Break Up and Disperse
- glyceryl monostearate (also pearlescent agent)
- lauramide DEA (also foam booster)
- polysorbates

Color Additives
(synthetic organic colors derived from coal and petroleum sources (not permitted for use around the eye except when permitted by specific regulations)
- D&C Red No. 7 Calcium Lake (lakes are dyes that do not dissolve in water)

Inorganic Pigments
(generally approved for general use in cosmetics, including for the eye area, except when not specifically permitted by color additive regulations)
- iron oxides
- mica (iridescent)

Others
- magnesium aluminum silicate—absorbent, anti-caking agent
- silica (silicon dioxide)—absorbent, anti-caking, abrasive
- sodium lauryl sulfate—detergent
- stearic acid—cleansing, emulsifier
- talc (powdered magnesium silicate)—absorbent, anti-caking
- zinc stearate—used in powder to improve texture, lubricates

—J.E.F.

"There are no standards for what natural means," says Bailey.

Anyone who has ever had poison ivy knows that "hypoallergenic" and "natural" are not necessarily interchangeable terms. Natural doesn't mean pure or clean or perfect either. According to the cosmetic trade journal *Drug and Cosmetic Industry*, "all plants [including those used in cosmetics] can be heavily contaminated with bacteria, and pesticides and chemical fertilizers are widely used to improve crop yields."

Likewise, there is no FDA definition of "non-comedogenic," a term used by the industry to indicate a product does not contain pore-clogging ingredients that could lead to acne.

For the most part, cosmetics sold in this country are safe when used according to directions. But FDA continues to be interested in hearing about problems that arise with them, no matter how rare. Such problems can be reported to your local FDA office, listed in the Blue Pages of the phone book, or to FDA's Office of Consumer Affairs at (1-800) 532-4440. ■

Judith E. Foulke and Isadora Stehlin are members of FDA's public affairs staff.

A Status Report On *Breast Implant Safety*

by Marian Segal

Signing a consent form is now part of the procedure for all women undergoing breast implant surgery. They also must be given information about the devices' known and possible risks.

Recently published studies have shown that women with silicone gel-filled breast implants do not have a greatly increased risk of typical autoimmune diseases, which were among the serious health concerns surrounding the devices. These include potentially fatal connective tissue diseases such as scleroderma and lupus erythematosus.

The new studies do not, however, rule out the possibility that a subset of women with implants may have a small increased risk of these conditions, or that some women might develop other immune-related symptoms that don't conform to "classic" disease descriptions.

PHOTO BY LAWRENCE RUGGERI

Between Jan. 1, 1985, and Sept. 17, 1996, FDA received 103,343 adverse reaction reports associated with silicone breast implants and 23,454 reports involving the saline implants.

Nor did the studies address other important safety questions, including implant rupture rates and the incidence of capsular contracture (shrinking of scar tissue around the implant, which can cause painful hardening of the breast or distort its appearance). Answers to these and other questions await the results of new or ongoing studies.

Widespread reports of adverse reactions to silicone gel-filled implants and a lack of evidence supporting their safety led the Food and Drug Administration to order the devices off the market in April 1992. They remained available only to women in clinical studies, mostly women seeking breast reconstruction after breast cancer surgery. Saline-filled implants were allowed to remain on the market for all uses.

Reasons for New Studies

Breast implants had been marketed since the early 1960s—several years before the first medical device law was enacted in 1976, charging FDA with regulation of medical devices. Every year, thousands of American women had implant surgery for augmentation (to enlarge or reshape their breasts) or for reconstruction following mastectomy (removal of the breast) to treat breast cancer. Most of the implants consisted of a silicone envelope filled with silicone gel; about 10 percent were filled with saline (salt water).

Under the 1976 law, implants and many other devices already in use were allowed to remain on the market, with the understanding that the agency would at some time ask manufacturers to submit scientific data showing these "grandfathered" products were safe and effective.

FDA requested this information for silicone gel-filled implants in April 1991 in response to a growing number of adverse reaction reports that raised safety concerns about the devices. The data submitted did not prove the devices safe, as required by law, so the agency restricted their use to clinical trials designed to resolve the safety questions.

Between Jan. 1, 1985, and Sept. 17, 1996, FDA received 103,343 adverse reaction reports associated with silicone breast implants and 23,454 reports involving the saline implants. Because these figures come from all databases, there may be a few duplicate reports. The reports included risks clearly associated with the devices, as well as adverse effects attributed to the implants, but not proved to be linked to them. (See "Known Risks of Breast Implants" and "Possible Risks of Breast Implants.")

Silicone Implant Studies

Some recent studies comparing the rates of immune-related diseases in women with implants versus those without implants have provided reassurance that women with implants are not at a greatly increased risk of these disorders.

The largest of these retrospective, or "look-back," studies is the Harvard Nurses' Health Study. The study used data from 87,501 nurses followed for other research purposes from 1976 through May 31, 1990, before there was widespread media coverage of the possible association between breast implants and connective tissue disease. None of the women had connective tissue disease at the start of the study.

In an article published in the June 22, 1995, *New England Journal of Medicine,* the researchers reported that 516 of the nurses had developed definite connective tissue diseases. Women with breast implants numbered 1,183. The types of implants included 876 silicone gel-filled, 170 saline-filled, 67 double lumen (silicone gel-filled implants with a saline-filled outer envelope), 14 polyurethane-coated, and 56 of unknown type. Only three of the 516 women with definite connective tissue diseases had implants (one silicone-gel filled, one

Polyurethane-Coated Implants

About 110,000 women have silicone gel-filled implants with a polyurethane coating, intended to reduce the risk of capsular contracture. In April 1991, an FDA analysis showed that polyurethane foam could break down under human body conditions to form a chemical called TDA, which can cause cancer in animals. As a result, the manufacturer immediately stopped selling the product.

Recently, however, a study to measure TDA in women with polyurethane implants found that a woman's risk of cancer from exposure to TDA released by the implant is negligible—about one in a million over a lifetime. FDA considers it unlikely that even one woman would develop cancer from these implants. The study supports the agency's original recommendation that women who are not having problems should not have the implants removed solely because of concern about cancer from TDA exposure. ■

—M.S.

***FDA** is requiring manufacturers to collect data on the saline implants as well, because the incidence of known risks is not well defined.*

saline, and one double lumen).

The authors reported they "did not find an association between silicone breast implants and connective tissue disease, defined according to a variety of standardized criteria, or signs and symptoms of these diseases."

Similarly, a 1994 study conducted at the Mayo Clinic found no increased risk of connective tissue diseases among implant recipients. The investigators based their conclusion on comparison of the medical histories of 749 women with breast implants in Olmsted County, Minn., with a similar group of women who did not have implants.

Although these studies did not find a risk increase, a retrospective study reported by C.H. Hennekens and colleagues in the Feb. 28, 1996, issue of the *Journal of the American Medical Association*, suggests a small increased risk of traditional connective tissue disease among women with the implants.

An immunology and epidemiology expert, S. Lori Brown, Ph.D., a research scientist officer in the epidemiology branch of FDA's Center for Devices and Radiological Health, explains that an inherent problem in the studies is that some connective tissue diseases are extremely rare. "If you have a disease that has an incidence of 1 in 100,000 in the general population, for example, and you do a study of 750 women with implants, like the Mayo Clinic Study, then you wouldn't really expect to see even a single case of that disease," she says,

Immunology Tests

Several laboratories are offering tests that claim to detect levels of antibodies to silicone that presumably indicate a leaking or ruptured implant.

FDA has not cleared or approved these tests for such purposes, and the agency has sent letters to several companies, warning of future regulatory action if they continue to promote the devices without a premarket approval application.

"There are important unresolved issues with these tests," says Peter Maxim, Ph.D., chief of the Center for Devices and Radiological Health's immunology branch of the division of clinical laboratory devices. "For one thing, the very existence of silicone antibodies has not been proven to the satisfaction of all scientists," he says. "Secondly, if antibodies are detected, is there in fact a correlation with the presence or the status of implants, or do they reflect prior environmental exposure? Silicone is in myriad products, including foods, medicines, and antiperspirants absorbed by the skin, to name a few."

The next problem, Maxim says, is that there are claims that extremely high antibody levels may indicate a leaking or ruptured implant. This, then, raises the question of what medical intervention, if any, should be taken.

Sahar M. Dawisha, M.D., a rheumatologist in FDA's division of general and restorative devices, adds that no one really knows what the clinical significance of an antibody to silicone means or at what level it is harmful.

"Furthermore," she says, "in autoimmune or connective tissue disease—where antibody tests are generally used—the presence of antibodies doesn't define the disease. A disease is defined by clinical signs and symptoms, and antibodies are used as supporting evidence."

Finally, John Nagle, consumer safety officer in the Center for Devices and Radiological Health's diagnostic devices branch, says, "The tests themselves may be harmless, but they sure are expensive, somewhere between $500 and $1,000," adding that "a lot of them are being done for litigation purposes rather than to help the patient medically." ■

—M.S.

Known Risks of Breast Implants

Surgical Risks

- possible complications of general anesthesia, as well as nausea, vomiting and fever
- infection
- hematoma (collection of blood that may cause swelling, pain and bruising, perhaps requiring surgical draining)
- hemorrhage (abnormal bleeding)
- thrombosis (abnormal clotting)
- skin necrosis—skin tissue death resulting from insufficient blood flow to the skin. The chance of skin necrosis may be increased by radiation treatments, cortisone-like drugs, an implant too large for the available space, or smoking.

Implant Risks

- capsular contracture (hardening of the breast due to scar tissue)
- leak or rupture—silicone implants may leak or rupture slowly, releasing silicone gel into surrounding tissue; saline implants may rupture suddenly and deflate, usually requiring immediate removal or replacement
- temporary or permanent change or loss of sensation in the nipple or breast tissue
- formation of calcium deposits in surrounding tissue, possibly causing pain and hardening
- shifting from the original placement, giving the breast an unnatural look
- need for repeat surgeries
- interference with mammography readings, possibly delaying breast cancer detection by "hiding" a suspicious lesion.

Also, it may be difficult to distinguish calcium deposits formed in the scar tissue from a tumor when interpreting the mammogram. *When making an appointment for a mammogram, the woman should tell the scheduler she has implants to make sure qualified personnel are on-site. At the time of the mammogram she should also remind the technologist she has implants before the procedure is done, so the technologist can use special techniques to obtain the best mammogram and to avoid rupturing the implant.* ■

—M.S.

Possible Risks of Breast Implants

- Autoimmune-like disorders—signs include joint pain and swelling; skin tightness, redness or swelling; swelling of hands and feet; rash; swollen glands or lymph nodes; unusual fatigue; general aching; greater chance of getting colds, viruses and flu; unusual hair loss; memory problems; headaches; muscle weakness or burning; nausea or vomiting; and irritable bowel syndrome.

Recent studies have shown, however, that there is not a large increased risk of traditional autoimmune, or connective tissue disease, from silicone gel implants.

- Fibrositis/fibromyalgia-like disorders (pain, tenderness and stiffness of muscles, tendons and ligaments). ■

—M.S.

Top: Silicone gel-filled breast implants.

Bottom: Saline-filled breast implants.

(Photos courtesy of Mentor H/S, Santa Barbara, Calif.)

"unless there's an exceedingly high—more than a hundredfold—increase in risk."

Small studies like these can rule out huge risks, but not smaller, yet significant risk increases that would only show up in studies that include several thousand women with implants, Brown says. Nor do the studies fully examine or answer whether the implants might in some women lead to symptoms not typical of classical disease manifestations.

Other Concerns

Brown also stresses that connective tissue diseases are not the only issue of concern, especially since they may affect a much smaller proportion of women with implants. The larger issue, she says, is the local complications that are clearly related to breast implants, such as rupture and migration of the silicone gel, capsular contracture, and infection.

"Of the two groups of women who consider getting implants—for breast reconstruction or for augmentation," Brown says, "the larger group wants them for cosmetic purposes. These are healthy women who may go out and get implants without a clear picture of what the possible risks are. They may end up going back in for surgery time and again and never be happy with the cosmetic effect."

In testimony before a congressional subcommittee in August 1995, FDA Commissioner David A. Kessler, M.D., stated that "Published studies to date suggest a rupture rate between 5 and 51 percent—an enormous range—and, unfortunately, we do not know with any confidence where within that range the real rupture rate lies." He also cited two studies that indicate the risk of rupture increases as the implants age.

Another concern—increased risk of breast cancer—has not been borne out by studies. "Several studies have indicated there is no increased risk of breast cancer in women with implants," Brown says. However, she adds, these women are not yet in the age group that is more prone to breast cancer, and it remains to be seen whether they will eventually have a higher incidence of breast cancer than women without implants. Long-term studies to look at this are under way.

The events that led to removal of silicone implants from the market made it clear that prospective, or forward-looking, studies were also needed to answer important safety questions.

Manufacturers' Studies

The events that led to removal of silicone implants from the market made it clear that prospective, or forward-looking, studies were also needed to answer important safety questions. Implant manufacturers agreed to conduct human trials in three phases: urgent need, adjunct, and core studies.

"The purpose of the first phase [urgent need] actually was simply to quickly provide implants to women who were already in the process of getting them for breast reconstruction or for another medical reason, and to bridge the time until the adjunct studies were begun," says Sahar M. Dawisha, M.D., a rheumatologist and medical officer who joined FDA's division of general and restorative devices in April 1993.

The women did, however, have to sign an informed consent form that summarized the risks and benefits of the implants. This form had not previously been required.

"The second phase, or adjunct, studies were intended to follow reconstruction patients for five years to assess short-term safety data, including rates of capsular contracture, rupture, and complications such as infection and hematoma [collection of blood that may cause swelling, pain and bruising]," Dawisha says. "These studies are open to all women wanting breast reconstruction with implants because of mastectomy, traumatic injury to the breast, or a disease or congenital disorder causing a severe breast abnormality. They do not include augmentation patients."

Mentor Corporation of Santa Barbara, Calif., began adjunct studies in 1992. According to Cathy Fox, clinical programs supervisor at Mentor, 14,803 patients are now enrolled.

The third phase, or core studies, Dawisha says, were intended to determine the full safety and effectiveness profile of the device, including rupture rates, quality-of-life benefits, extent of interference with mammography, and many more safety concerns—including rheumatologic assessments—that would need a large number of women. They were also to include augmentation patients. The sponsors, however, have not initiated these studies.

Saline Implants

Although many of the local complications of gel-filled implants are also associated with saline implants, the latter were permitted to remain on the market unrestricted for both reconstruction and augmentation. FDA considers saline-filled implants less risky, because although they have the same silicone rubber envelope as gel-filled implants, leakage or rupture would release only salt water, not silicone gel, into the body.

Nevertheless, FDA is requiring manufacturers to collect data on the saline implants as well, because the incidence of known risks (for example, deflation and capsular contracture) is not well defined. When the Medical Device Amendments were passed, it was determined that these devices would also eventually require premarket approval. In January 1993, FDA notified saline implant manufacturers that they would have to submit safety and effectiveness data for their products. In December 1994, the agency told them what type of safety and effectiveness data were needed, and delineated objectives and time frames for the trials.

Saline implants will stay on the market while studies are conducted, but the companies must report laboratory, animal and clinical data in stages, and must provide written information on known and possible risks of their products.

Women considering saline implants can ask their doctors for a copy of the manufacturer's information sheet, a copy of the product insert sheet for the specific implant to be used, and a copy of the hospital informed consent form. Women can also ask their physicians about participating in the saline breast implant trials.

Brown hopes that further studies will more clearly define risks associated with all types of implants.

"We need to be able to tell women considering breast implants—whether for augmentation or reconstruction—the specific risks on which they can base their decision," she says. "It should be made clear that implants do not last forever, that they may break, and in what time period it is thought they might break. Most women have no idea implants break and there's very little information about rupture rates.

"The same is true for other complications, some of which may require further surgery or may cause the woman to be displeased with the cosmetic effect, which, of course, is the reason she got them," Brown says. "For a product that a person is putting in her body presumably for 20 years or more, we should have this information." ■

Marian Segal is a member of FDA's public affairs staff.

For More Info

To obtain a comprehensive information packet on breast implant issues, request "Breast Implants, An Information Update" by calling the agency's breast implant information line at (1-800) 532-4440. On-line information is available at *http://www.fda.gov/oca/breastimplants/bitac.html* on the agency's Web site. ■

Help for Urinary Tract Infections

by Evelyn Zamula

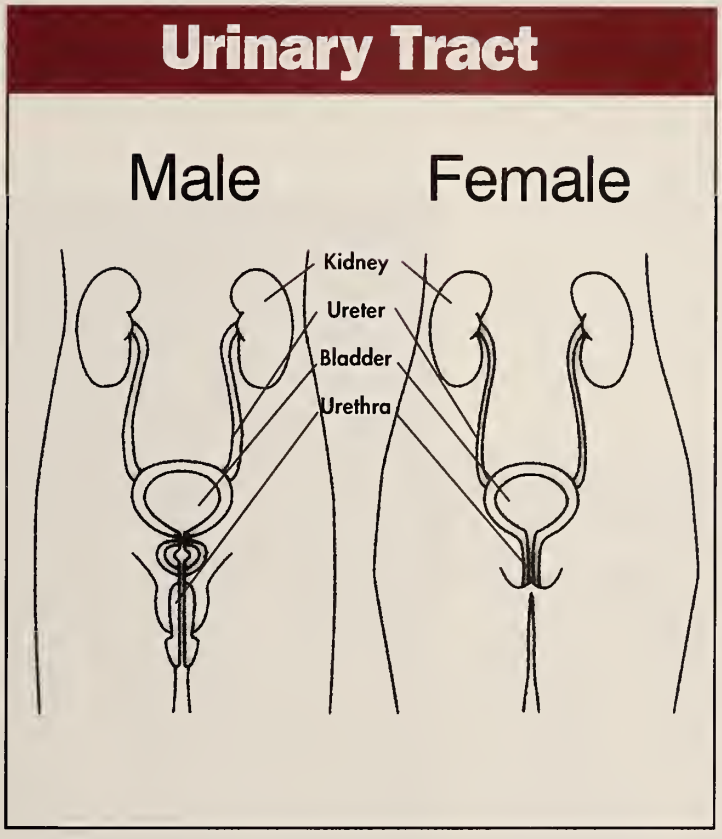
Though men don't escape urinary tract infections, women get the lion's share of UTIs, about 25 times more often than men. Most of these infections are uncomplicated: They occur in otherwise healthy women and girls who have normal urinary tracts and normal urinary functioning and no underlying physical problems.

The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health estimates that by age 30, half of all women experience at least one UTI, and about 20 percent of these women will have recurrent UTIs. Each year, UTIs are responsible for more than 6 million doctor visits and about $4.5 billion in health-care costs. Only upper respiratory tract infections account for more absenteeism in working women.

The urinary tract consists of the kidneys, ureters, bladder, and urethra. The kidneys—bean-shaped organs weighing about 4 to 6 ounces in the adult and located below the ribs toward the middle of the back—filter liquid waste from the blood that passes through them to produce urine. Urine passes from the kidneys down through two narrow tubes called ureters to the bladder, a triangular-shaped organ in the lower abdomen. The bladder acts as a reservoir for urine until it is emptied out through the urethra, a tube leading from the bladder to outside the body.

When limited to the urethra, an infection of the urinary tract is called urethritis. More often than not, however, bacteria travel up a woman's one-and-a-half-inch-long urethra to the bladder, where they may cause cystitis, the most common urinary tract infection. A more serious condition called pyelonephritis can result when bacteria from the bladder ascend to the kidneys via the ureters.

Before the modern drug era, doctors prescribed the urinary antiseptic Mandelamine (methenamine mandelate), cranberry juice, and diets that acidified the urine to prevent and treat recurrent UTIs. In many cases, this treatment was ineffective, and women who had recurrent UTIs ultimately suffered kidney failure. By the 1940s, the antimicrobial sulfa drugs had been introduced and proved very effective in treating UTIs. The explosive development of broad-spectrum antibiotics that began about the same time with the discovery of penicillin—and continued with the development of tetracyclines, erythromycin and cephalosporins—provided more options in treating UTIs.



The kidneys filter liquid waste to produce urine, which passes through the ureters to the bladder. The bladder acts as a reservoir for urine until it leaves the body through the urethra. Infections can occur anywhere in the urinary tract, but are most common in the bladder.

Newer Drugs

Some oral antibiotics, such as nitrofurantoin (marketed as Macrodantin and Furadantin), are indicated specifically for urinary tract infections, as are some combination antibiotics such as trimethoprim and sulfamethoxazole (marketed as Bactrim, Septra, and others). In addition, FDA has approved a group of drugs called quinolones (including ciprofloxacin [Cipro], enoxacin [Penetrex], norfloxacin [Noroxin], ofloxacin [Floxin], cinoxacin [Cinobac], and lomefloxacin [Maxaquin]) for treating UTIs. Philip Hanno, M.D., chairman of the urology department and professor of urology at Temple University, Philadelphia, Pa., says that with quinolones, "... you don't have to bring people into the hospital to get good levels of antibiotics that can treat pseudomonas and other gram-negative organisms. Previously, we had to use parenteral antibiotics [intravenous medications]. I do think they're overused, though, and resistance to them is developing."

Each group of drugs affects bacteria in the urine differently, either by interfering with reproduction, or depriving them of certain enzymes necessary for their growth. Successful treatment depends on the concentration of the bacteria-fighting drug in the urine.

Normal urine is sterile. An average adult passes about 3 pints of urine each day, but the amount varies, depending on how much food and drink are consumed.

The urinary system is constructed to repel infection. Valve-like structures at the lower ends of the ureters prevent urine from backing up (called vesicoureteral reflux) into the kidneys, where it could cause damage. When infection occurs, urination helps wash bacteria out of the bladder.

Symptoms of Infection

Sometimes a person can have a UTI without having symptoms. But usually UTIs are accompanied by such discomforts as pain and a burning sensation during urination, frequent urination—often passing no more than a few drops at a time—and a feeling that the bladder doesn't feel empty even after urinating. The urine may look cloudy, or may have

How Women Can Prevent Urinary Infections

Here are some suggestions to help prevent UTIs:

• Drink at least eight glasses of water a day, in addition to the coffee, tea, cola drinks, and other beverages you normally drink. Frequent urination flushes bacteria out of the bladder and makes urinary symptoms more bearable. Some doctors advise drinking large amounts of cranberry juice, which acidifies the urine and makes it less hospitable to bacteria.

• Wipe from front to back to prevent bacteria in the anal area from entering the vagina and urethra.

• Empty the bladder shortly before and after sex.

• Wash the genital area before sex with plenty of warm water. Bacteria from the vaginal, anal and perineal areas can be introduced into the urethra during sex.

• Check with your gynecologist if you suspect a diaphragm is contributing to your problems. You may need another size, or perhaps another method of birth control.

• Use some sort of water-soluble lubricant, such as a vaginal jelly (not petroleum jelly), if your vagina feels dry and uncomfortable during sex, especially if you're past menopause. Bruised tissues may become irritated, even infected.

• Avoid using feminine hygiene products, such as sprays, deodorants or douches, which may irritate the urethra.

• Change sanitary pads and tampons frequently during menstruation.

• Avoid using hot tubs—because the water is not hot enough to kill bacteria—and highly chlorinated pools, because too much chlorine may irritate the genital area.

• Don't use perfumed toilet paper or heavily scented soaps and powders in the vaginal area, or take bubble baths. (Some bubble bath products warn that they can cause urinary tract irritation.) Some laundry detergents, bleaches, and fabric softeners leave residues that can be irritating or cause allergic reactions. Try unscented laundry detergents or soaps if you are sensitive.

• Take showers instead of baths, because showers wash bacteria away.

• Avoid wearing tight jeans, body suits and pantyhose. The heat generated by tight clothing makes it easier for bacteria in your genital area to grow. Replace nylon underclothing with cotton underwear. ■

—*E.Z.*

PHOTOGRAPH BY NORMAN WATKINS

a bloody tinge. A person with a UTI may feel tired and shaky, sick all over. Often, women feel pressure above the pubic bone and men feel fullness in the rectum. Chills and fever, flank pain, nausea, and vomiting suggest kidney involvement.

Common Culprits

Many bacteria can cause UTIs in women, but the most common are *Escherichia coli* (*E. coli*), responsible for over 80 percent of infections. Normally, these bacteria reside in the gastrointestinal tract, but they may also be present in the vaginal and rectal areas, and on the skin of the perineum, the band of flesh between the anus and the vagina. The sexually transmitted microorganisms *Chlamydia trachomatis* and T-mycoplasma (*Ureaplasma*) can cause UTIs in both men and women. These infections are usually confined to the urethra and reproductive organs.

Women can acquire UTIs after sexual intercourse. Many women have their first bout of cystitis after they become sexually active; in fact, "honeymoon cystitis" was once a common name for this affliction. Data from a variety of studies suggest that during sexual intercourse, bacteria in the vaginal area can be pushed into the urethral opening and move up into the bladder, making it one of the most important risk factors for developing uncomplicated UTIs.

Using a diaphragm for contraception can be an additional risk factor for UTIs. The diaphragm may press on the neck of the bladder, preventing it from emptying completely and leaving a pool of stagnant urine for bacteria to grow in. Bacteria may also enter the urinary tract when the diaphragm is inserted and removed and when it is left in place longer than recommended by the labeling or the doctor. Researchers have found an association between UTIs and sexual intercourse when women use a spermicide or a diaphragm/spermicide or when their partners use a condom with spermicidal foam. Thomas Hooton, M.D., and Walter Stamm, M.D., in the March 1991 issue of *Medical Clinics of North America Studies* report that spermicides increase colonization of the vagina with bacteria, thus increasing the risk of bladder infection.

Pregnant women get about the same number of UTIs as nonpregnant, sexually active women of childbearing age. However, when a pregnant woman gets a UTI, it is more likely to travel upwards to the kidneys. Since a woman can have bacteria in her urine, but no symptoms, it's important that urine cultures be performed on the first prenatal visit and at intervals thereafter. Studies have shown an association between bacteria in the urine in the first trimester and the subsequent development of acute pyelonephritis. Pregnant women with UTIs can be treated with antibiotics, but, as always, the drug's effectiveness, the stage of pregnancy, the mother's health, and the potential effects on the fetus have to be carefully considered. Tetracyclines, cotrimoxazole, nitrofurantoin, and quinolones are not recommended for pregnant women.

Not all UTIs are a result of sexual activity. Another common source of infection is the catheter, a tube that is placed in the bladder to drain off urine when a patient is unconscious, very ill, recovering from surgery, or incontinent. About 900,000 UTIs are contracted in hospitals each year, and up to 90 percent of these infections are associated with indwelling catheters. Avoiding unnecessary catheter-

A common source of urinary infection is a catheter (tube) inserted in the bladder to drain urine during hospitalization.

ILLUSTRATION BY JACK PARDUE

ization is the best way to prevent such UTIs. When a catheter is necessary, strict antiseptic techniques must be used by medical personnel when inserting and maintaining this device to prevent the introduction of bacteria into the bladder.

Diabetics run a higher risk of UTIs because their immune systems are suppressed. Additionally, their urine is rich in glucose, which is a good growing medium for any bacteria that enter the bladder.

Diagnosis

Though a urinalysis can tell the doctor bacteria are present in the urine, only a urine culture can identify the particular organism. Which drug will be effective and the length of time it is used depend both on the patient's history and what the culture reveals. Since a UTI can cause excruciating discomfort—and since many medications are effective against a UTI—most doctors prefer to treat patients with symptoms without waiting the 48 hours or so for culture results. The medication can be changed at that time, if necessary.

Patients should report all known allergies, such as an allergy to penicillin or sulfa drugs, to the doctor before treatment begins.

Types of Therapy

Doctors can use single-dose therapy, a three-day course of drugs, or a longer regimen. Studies have shown that a single dose of trimethoprim or cotrimoxazole, for instance, is effective in treating uncomplicated bacterial cystitis and asymptomatic bacterial infections in sexually active women and in girls with normal urinary tracts. Not only do single-dose therapies save money, but they are simple to take—thus promoting compliance—well-tolerated, and preferred by patients. In addition, they produce fewer side effects and less risk of developing resistant organisms. And, for pregnant women, a single dose of some drugs also poses less danger to the fetus.

Not all urologists like single-dose therapy. "I rarely use it," says Dr. Hanno, "unless it's someone who's very responsible and has not had symptoms for a long time—generally people who are on self-treatment programs—and won't panic if symptoms don't go away after one dose. Then they can take one dose of medicine and that's it. But since it usually takes two or three days for the symptoms to go away even if you sterilize their urine with one dose, you know that they're going to call you back after taking one pill. I find it makes more sense to put people on the three-day therapy."

Which drug will be effective and the length of time it is used depend both on the patient's history and what the culture reveals.

Urologists deal with recurrent UTIs in several ways. When women have three or more symptomatic UTIs a year, some urologists may prescribe low doses of an antimicrobial drug, such as trimethoprim/sulfamethoxazole or nitrofurantoin, to be taken daily for six months or longer as a preventative. Taken at bedtime, the drug remains in the bladder the whole night and is thus more effective. Other urologists prefer to give their patients medications to be taken on alternate nights or even three nights a week. When sexual intercourse is the culprit, one dose of an antibiotic after sex has proved a safe, effective and inexpensive treatment for preventing recurrent urinary tract infections.

Since illness is apt to strike at inconvenient times, women subject to recurrent UTIs often panic when they feel symptoms coming on and don't have immediate access to a doctor. "What most urologists do, once we have established that it's a recurrent urinary infection from reinfection—which makes up about 99 percent of UTIs in women—is give them a prescription to keep with them," says Hanno. "At the first sign of infection they take antibiotics for three days. If symptoms don't get better in three days, then it's worthwhile to do a urine culture, to see if something unusual is going on."

When infections persist despite treatment and are caused by the same strain of bacteria, the doctor checks for problems in the urinary system. The intravenous urogram (often incorrectly called the intravenous pyelogram) is an important diagnostic tool: The radiologist injects an iodine-containing liquid dye into the veins. As the dye concentrates in the kidneys and urine and flows through the ureters and bladder, x-ray pictures are taken that outline the urinary tract and reveal any abnormalities.

Another valuable test—especially for babies and people who cannot tolerate the dye used in the intravenous urogram—is done by ultrasound, which gives pictures from the echo patterns of sound waves bounced back from the urinary organs. Doctors may also perform a cystoscopy, where they look into the bladder with a cystoscope, an instrument made of a hollow tube with several lenses and a light source. The doctor can see tumors or other lesions in the bladder, or sediment from urinary stones.

Fortunately, most UTIs don't require such measures. Most healthy adults with normally functioning urinary tracts who have UTIs can be safely and effectively treated with a variety of medications. And, with prompt treatment, they will experience no long-term damage to the urinary system. ■

Evelyn Zamula is a writer in Potomac, Md.

OVARIAN CANCER

by Marian Segal

Early detection and treatment can mean the difference between life and death.

She crowned herself "the Queen of Neurosis," but this time, it was not simply an overactive imagination that made her fear for her health. It was symptoms of the ovarian cancer that eventually claimed her life.

Gilda Radner, one of the original Not Ready for Prime Time Players of television's "Saturday Night Live," claimed in her book *It's Always Something* that she could get neurotic over any health problem. "I hated to be sick and I had an imagination that could turn a stomachache into the plague."

So, she wrote, when a complete physical examination in January 1986 failed to explain the overwhelming fatigue and general malaise she was feeling, she agreed with the doctor that her symptoms might just be from depression; she had, after all, been going through a rough period in both her personal and professional life. It was not until October—10 months and several symptoms, diagnoses, and failed therapies later—that cancer of the ovaries was confirmed.

Delay in diagnosing ovarian cancer is not unusual. Early detection is difficult because disease confined to the ovary seldom produces symptoms. When symptoms do surface, they are often vague and easily mistaken for other, often minor, ailments.

Radner's cancer was not discovered until it had spread to her bowel and liver. She suffered from fatigue, low-grade fever, pelvic cramping, abdominal bloating, gas, and aches and pains in her upper thighs and legs. Loss of appetite and a feeling of fullness, indigestion, nausea, weight loss, and, less often, vaginal bleeding and low back pain are other symptoms.

As the tumor grows, it may press on the bowel and bladder, causing constipation and frequent urination. Malignant cells can break away from the tumor and spread directly to other organs in the abdomen, such as the stomach, colon and diaphragm (muscle separating the chest cavity from the abdomen), causing a fluid buildup that results in swelling and discomfort. The cells can also enter the bloodstream or lymph system and spread to other parts of the body.

Radner wrote that her complaints had

The late Gilda Radner (top center) puts on a funny face in 1975 with fellow "Saturday Night Live" Not Ready for Prime Time Players (clockwise) Garrett Morris, Dan Aykroyd, Jane Curtin, Laraine Newman, Chevy Chase, and the late John Belushi. (Courtesy NBC PHOTO)

been variously attributed to Epstein-Barr virus infection, depression, stress, and anxiety. She had undergone blood tests, a barium enema, and ultrasound (pelvic sonogram). According to Radner, the sonogram, done in the summer of 1986, showed "congestion" and the "ovaries weren't exactly in the place they were supposed to be, but that wasn't serious." There was no sign of tumor or bowel obstruction.

Aspirin to Acupuncture

Attempting to combat her ills through both mainstream and holistic medicine, Radner tried remedies that ran the gamut from aspirin, anti-inflammatories and antidepressants to health foods, vitamins, acupuncture, and colonics (unconventional type enemas).

"Suddenly, I began to wonder how to please so many people," she wrote. "Do I take the magnesium citrate? What about the coffee enema? Do I do both? Do I do the abdominal massage or the colonic? Do I tell the doctors about each other?"

Then, late in October, an abnormal liver function test prompted more exams. A CAT scan and analysis of fluid from the abdomen confirmed ovarian cancer.

Diagnosed at age 40, Radner was younger than most women with the disease. The chance of developing ovarian cancer increases with age; most cases are found in women who have gone through natural menopause, with the average age at diagnosis being 61. As was true with Radner, however, women with a family history of the disease generally are diagnosed at a younger age.

Each year in the United States, ovarian cancer is diagnosed in about 26,000 women and claims more than 14,000

The risk of ovarian cancer is reduced in women who have had multiple pregnancies and in those who used birth control pills.

lives. It is most common in women living in Europe and North America; Asian women have a relatively low incidence. Although Chinese and Japanese women living in the United States have higher rates of ovarian cancer than their counterparts in Asia, the disease is still less common among this group than among the native white population in the United States. Rates among black women in all parts of the world are low.

Certain factors are associated with an increased risk of getting ovarian cancer. Although the lifetime risk for most women is 1 in 70, it doubles for women who have never been pregnant. Also at increased risk are women who have had breast, intestinal, or rectal cancer. Under investigation as possible risk factors are: high-fat diet, early onset and late cessation of menstruation, being of Eastern European Jewish descent, and use of talcum powder in the genital area.

Women with close relatives who have had ovarian cancer are also at greater risk, reaching perhaps a 50 percent chance if they have at least two first-degree relatives (mother, sister or daughter) with the disease. This compares with a 1.4 percent chance in women without a family history. Women who have a first-degree relative and one or more second-degree relatives (aunt, grandmother) who had ovarian cancer have a somewhat lesser risk than those with two first-degree relatives, but are still considered to be at high risk. Radner wrote that her mother had breast cancer and a cousin had both breast and ovarian cancer. Later, it was learned that other of her relatives had ovarian cancer as well.

About 5 to 7 percent of all ovarian cancer is thought to be inherited. In 1994, scientists identified a gene, which they named BRCA1, that related to the development of inherited breast cancer. Changes or abnormalities in this gene are now also considered responsible for about 80 percent of inherited ovarian cancer. The abnormal gene can be inherited from either parent.

The Gilda Radner Familial Ovarian Cancer Registry, established in 1981 at Roswell Park Cancer Institute in Buffalo, N.Y., and named for Gilda Radner after her death in 1989, included 2,946 cases of ovarian cancer in 1,346 families as of January 1997.

Reduced Risk

Factors associated with a reduced risk of ovarian cancer include: giving birth to more than one child, breast-feeding, tubal ligation (female sterilization), and use of birth control pills.

Evidence suggests that hormones may influence development of the disease. The risk of ovarian cancer is reduced in women who have had multiple pregnancies and in those who used birth control pills. The Cancer and Steroid Hormone Study by the national Centers for Disease Control and Prevention and the National Institute of Child Health and Human Services found that use of oral contraceptives for even a few months reduced the risk of ovarian cancer by 40 percent in women 20 to 54 years old.

The study, published in the March 12, 1987, *New England Journal of Medicine*, also found that the longer a woman used birth control pills, the lower her risk of ovarian cancer, and that the protective effect persisted long after stopping the pill. Based on these data, since 1989, the labeling for oral contraceptives has included decreased incidence of ovarian cancer among the noncontraceptive health benefits of the pill.

On the reverse side of the coin, in January 1993, FDA requested that drug firms revise fertility drug labels to include ovarian cancer as a potential adverse drug reaction. The action was in response to a report in the November 1992 issue of the *American Journal of Epidemiology* suggesting a possible relationship between use of fertility-enhancing drugs and ovarian cancer. The analysis was based on data from 12 studies comparing women with ovarian cancer to those without the disease. Only three of the studies, however, contained data on the use of fertility drugs and risk of ovarian cancer. (A 1987 article in the same journal reported no association between the drugs and ovarian cancer.)

FDA urged caution in interpreting the findings of the 1992 report because the analysis only included small numbers of women and because the article gave no information about the fertility drugs prescribed, reasons for the infertility, or tumor size or stage of disease at diagnosis.

Search for a Screening Test

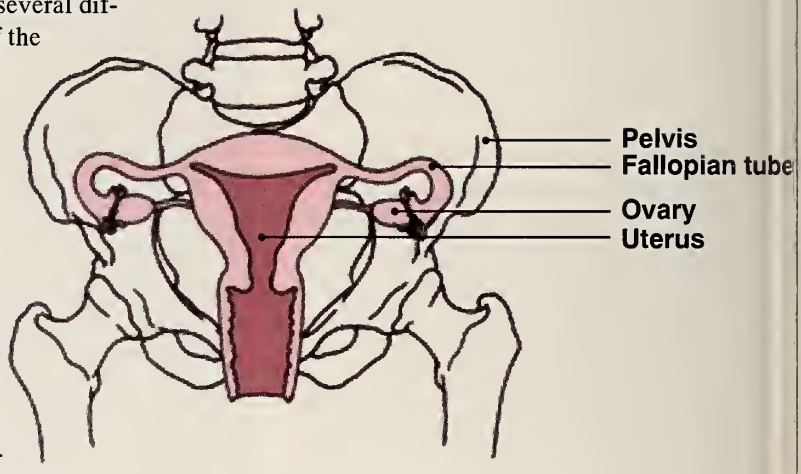
According to the registry, if ovarian cancer is diagnosed while still confined to the ovaries, the chance for cure is 85 to 90 percent. According to the American Cancer Society, only 23 percent of all cases are diagnosed at this early stage. Among women whose cancer has spread beyond the ovary by the time it's diagnosed, only 20 to 25 percent survive five years. However, unlike cervical or breast cancer (which may be detected early by a Pap test or mammogram, respectively), ovarian cancer has no approved screening test, though some are under investigation.

"The traditional routine pelvic examination is largely ineffective for early detection," says Julie Beitz, M.D., a medi-

The Ovaries—How They Work

The ovaries are located in the pelvis, one on each side of the uterus. About the size and shape of almonds, they are made up of several different cell types. Some carry out the hormonal functions of the organ, while others provide physical support. The ovaries have two main functions:

- ovulation (the release of an egg each month)
- production of estrogen and progesterone, hormones that regulate the menstrual cycle and pregnancy and control the development of female physical traits, such as the breasts, pelvic structure, fat distribution, and body hair.



From birth, the ovaries contain the cells that eventually become ova (eggs). Each month, beginning with puberty and until menopause, hormones produced by the pituitary gland in the brain stimulate ovulation (release of an egg), which alternates each month between the two ovaries. (Not all women ovulate every month.)

The egg travels through the fallopian tube to the uterus. If it is fertilized, it may grow and develop in the womb. If not, hormone changes cause shedding of the uterine lining, and menstruation begins about two weeks later. ■

—M.S.

cal oncologist in FDA's division of oncology and pulmonary drug products. "Often you can't feel a normal-sized ovary. And even if you can, it's hard to tell if it's enlarged because ovaries vary in size from person to person and day to day. Ovarian cancers start very small, and by the time they're large enough to feel, the cancer is most likely already advanced." The problem with ovarian cancer, she says, is that "you have to detect very small changes, and these are hard to detect on a pelvic exam because it's a very indirect examination."

Researchers are working on developing an accurate test for the BRCA1 gene. At the time this special issue went to press, the American Society of Human Genetics recommended that testing for BRCA1 be limited to research in which subjects are members of families at high risk for either ovarian or breast cancer.

Researchers continue looking for tumor markers—substances that may appear in abnormal amounts in the blood or urine—that may prove useful in developing a screening test.

One such marker is CA 125, a substance in the blood that is elevated in patients with advanced ovarian tumors. Doctors now measure CA 125 levels in patients treated for advanced disease to determine if the tumor has shrunk or if disease has recurred. Its value in monitoring treatment prompted scientists to study its potential for early detection. Its use for screening, however, is investigational.

Transvaginal ultrasound is also being studied as a screening tool. With ultrasound, high-frequency sound waves are projected into the body, and the echoes produced are converted by computer into a picture. Unlike abdominal ultrasound, in which the sound wave-emitting device is placed on the outside of the belly, transvaginal ultrasound uses a probe placed in the vagina that can reach within millimeters of the ovaries, producing more detailed images.

"There is uncertainty as to the value of these tools as screening tests and their ultimate impact on mortality," says John Gohagan, Ph.D., chief of the National Cancer Institute's Early Detection Branch in the Division of Cancer Prevention and Control. NCI is conducting a clinical trial including 74,000 women aged 60 to 74 to clarify the issue. The trial is designed to assess the value of CA 125 and transvaginal ultrasound for early detection of ovarian cancer and to measure their impact on mortality.

Women in the trial are randomly assigned to either a screening group or a control group of 37,000 women each. The screening group will have periodic pelvic examinations along with CA 125 and transvaginal ultrasound tests. The control group will have routine medical care.

The only sure way to diagnose ovarian cancer is through microscopic examination by a pathologist of abnormal-looking fluid or tissue.

Diagnostic Procedures

If a woman or her doctor suspects ovarian cancer, diagnosis begins with a medical history of the patient, review of her symptoms, and complete physical examination, including a pelvic exam, in which the physician feels the vagina, ovaries, fallopian tubes, bladder, and rectum to check for any growths. A Pap test may also be done because, even though it cannot reliably detect ovarian cancer, it may detect cancer cells that have migrated to the uterine cervix from the ovaries.

Blood and urine tests may also be done, as well other procedures, depending on the woman's symptoms and results of her physical exam. These procedures include:

- *abdominal or transvaginal ultrasound*—helps distinguish fluid-filled cysts from a solid tumor
- *CAT scan*—produces x-ray images of cross-sections of body tissues
- *lower GI series (barium enema)*—visualizes the bowel on x-ray to detect abnormal areas that may be caused by ovarian cancer
- *intravenous pyelogram (IVP)*—produces x-ray pictures of the kidneys, bladder and ureters (tubes carrying urine from the kidneys to the bladder). Often, ovarian cysts or tumors can cause pressure on these organs, which may show up on an IVP.

The only sure way to diagnose ovarian cancer, however, is through microscopic examination by a pathologist of abnormal-looking fluid or tissue. While fluid can sometimes be obtained by needle aspiration or other techniques, more commonly a laparatomy or laparoscopy is done. Laparotomy is an exploratory operation in which the surgeon examines the abdomen thoroughly and removes fluid or tissue for examination. In laparascopy, a flexible, lighted tube is passed through a small incision in the abdomen, allowing the surgeon to examine the area and extract tissue for a biopsy.

If cancer is suspected, the surgeon usually removes the entire affected ovary to avoid cutting through the outer layer, which might cause the tumor to spread.

The tissue is sent to the pathologist for immediate evaluation, and if cancer is confirmed, the surgeon nearly always removes the second ovary, the uterus, and the fallopian tubes. Samples are taken of nearby lymph nodes, the diaphragm, the omentum (a fold of membranous lining in the abdominal cavity), and fluid from the abdomen to see whether the cancer has spread. If no fluid is found, several "washings" are taken: A saline solution is put into the abdomen and then removed to be examined for cancer cells. If there are suspicious lesions, tissue samples are also taken from the liver, small intestine, and large intestine.

Early Treatment Crucial

Trusting her instincts may have saved Jessica Marsh's life. Due in part to her own vigilance and persistence, Marsh (not her real name), a secretary in Rockville, Md., was diagnosed before her cancer had spread beyond the ovary, affording her a brighter prognosis.

For three months in the fall of 1985, Marsh, then 36 years old, had noticed pains in her right side around the time of her menstrual periods. Although the pains were brief and not severe, she decided to have her doctor check it out. A week or so before her appointment, however, a very sharp pain prompted her to call the doctor again. Her gynecologist was out of town, but the doctor on call had her come in.

"He told me that my stomach was distended, gave me a pelvic exam, and then congratulated me, telling me I was three months pregnant," Marsh recalls. "I told him I wasn't pregnant, that I already had two children and knew what it was like to be pregnant, and this was not a pregnancy."

At Marsh's insistence, the physician arranged for her to have a pelvic sonogram that day at a local hospital.

"I had the sonogram and the next thing I knew, the doctor who had examined me at the office came in, repeated the sonogram, and told me there was a mass and he wanted to do some more tests. The next morning, I had surgery to remove my ovaries, uterus, and fallopian tubes."

Although Marsh's experience may not be typical, it illustrates again the difficulty in correctly diagnosing the disease early. Yet, early detection and treatment can mean the difference between life and death.

Treatment Options

Ovarian cancer is always treated surgically, removing as much tumor as is feasible. Chemotherapy (drug treatment) or radiation therapy, or both, may also be given, depending on the extent of disease. Ovarian tumors usually grow outward, with an irregular, cauliflower-like shape. When the cancer spreads, parts of the tumor break off and attach to nearby organs. Cells may then spread to lymph nodes and distant organs.

Cancer limited to the ovaries may be successfully treated with surgery alone,

removing the ovaries, fallopian tubes, omentum (a fold of tissue attached to organs in the abdominal cavity), and uterus. Some patients may also receive chemotherapy or radiation therapy to kill any cancer cells remaining after surgery.

Disease that has spread beyond the ovaries almost always requires chemotherapy or radiation therapy in addition to surgery. Radiation therapy may be given by placing a radioactive solution into the pelvis and abdomen through a thin tube, coating the organs and total abdominal contents. Less commonly, external radiation using high-energy x-rays directed to the pelvis and abdomen may be prescribed.

The type of drugs used in chemotherapy depends not only on the extent of disease, but also on the type of cancer. About 85 to 90 percent of ovarian cancers arise from epithelial cells, which form the outer layer of the ovary. The rest derive from other cell types that make up the organ.

FDA has approved several drugs to treat ovarian cancer. Two of the most commonly used are Platinol (cisplatin) and Taxol (paclitaxel). Taxol was approved in December 1992 for advanced ovarian cancer that has not responded to other therapies or has progressed after treatment (see "Taxol's Long History"), and is being evaluated for first-line treatment. National Cancer Institute and FDA scientists cooperated in studies to evaluate the safety and effectiveness of Taxol. FDA's research role in drug development is a fairly new concept, designed to help speed the approval process for drugs for life-threatening diseases.

"It's a commitment by the agency to do more than just wait for packages of data to come in [from the drug's sponsor] and review them for approval," says Jerry M. Collins, Ph.D., director of the division of clinical pharmacology research in the Center for Drug Evaluation and Research. "We can't do this for every new drug in every therapeutic area," he says, "but for AIDS and cancer, we have done similar research before."

Since Taxol is given in combination with several other drugs, there was major concern about the potential for serious drug interaction. However, according to Collins, this research demonstrated that "paclitaxel actually had a lower risk of metabolic interactions than most other drugs."

Other chemotherapeutic agents used to treat ovarian cancer include Cytoxan and Neosar (cyclophosphamide), Paraplatin and Adriamycin (doxorubicin), and Hexalen (altretamine). A recent addition is Hycamtin (topotecon, approved in 1996 to treat ovarian cancer that recurs after other chemotherapeutic agents have failed. Hycamtin is the first of a new class of drugs called topoisomerase I inhibitors. They kill cancer cells by inhibiting an enzyme essential to the replication of human DNA.

Side Effects

Surgery, the first-line treatment for ovarian cancer, requires several days' hospitalization and a recuperative period of from four to six weeks. Removing the ovaries, which are the main source of the female hormones estrogen and progesterone, causes immediate menopause, and the symptomatic hot flashes are more severe than when menopause occurs more gradually, as it usually does naturally.

Radiation therapy can cause mild skin reactions, such as redness and drying in treated areas, urinary discomfort, diarrhea, and vaginal dryness. (Menopause can also cause vaginal dryness.) A small percent of patients may develop bowel obstruction, sometimes requiring surgical correction.

Other possible side effects of radiation therapy, commonly experienced with chemotherapy as well, include loss of energy and appetite, nausea, and vomiting.

Chemotherapy may also cause mouth sores, hair loss, and reduced platelet and blood cell counts that can lead to infections, anemia or bleeding. The drugs

ILLUSTRATION BY JACK PARDUE

Benign Ovarian Cysts

Noncancerous ovarian cysts are a very common condition among women of reproductive age. But before diagnosing a condition as a benign ovarian cyst, doctors rule out cancer.

Normally, the follicle (or cyst) created by the ovaries each month bursts harmlessly when ovulation occurs. (See "The Ovaries—How They Work.") Sometimes, however, this normal physiologic process goes awry. The follicle, instead of bursting and releasing its egg, may continue to swell with fluid, or the corpus luteum (tissue that secretes hormones to prepare for pregnancy) may fail to dissolve even though the egg has not been fertilized. In either of these situations, the result is a "functional," or physiologic, cyst—a fluid-filled sac that may be as small as a grape or as large as a grapefruit.

Functional cysts are the most common ovarian cysts. In a premenopausal woman, such a cyst is always benign (noncancerous) and will frequently disappear spontaneously within a couple of months. Sometimes a functional cyst ruptures, spilling ovarian fluid into the abdominal cavity and causing pain. As the body absorbs the fluid, however, the pain subsides, and surgery is rarely necessary.

Ovarian cysts may be diagnosed by pelvic examination or by ultrasound imaging. A woman who has a functional cyst may have abdominal cramps, nausea, and menstrual irregularity. However, many women have no symptoms at all.

A gynecologist who diagnoses a cyst of less than 6 centimeters (2 1/4 inches) in diameter in a premenopausal woman who is ovulating will usually want to observe the patient for a couple of menstrual cycles to see if the cyst goes away by itself, says Lisa Rarick, M.D., director of FDA's division of reproductive and urologic drug products.

If the cyst doesn't disappear spontaneously, the doctor may recommend that the woman take birth control pills to suppress ovulation. Most birth control pills are combinations of two female sex hormones, estrogen and progestin. In some cases, progestin-only pills (also called "mini-pills") may be prescribed instead of combination pills. Both combination birth control pills and mini-pills work by preventing the release from the brain of other hormones that stimulate ovulation. Deprived of hormonal stimulation, a functional ovarian cyst will often shrink and eventually disappear.

An ovarian cyst that doesn't disappear after a couple of months may be a benign semisolid cyst. This kind of cyst is usually diagnosed by ultrasound imaging. The most common semisolid cyst is a dermoid cyst, so-called because it is made up of skin-like tissue; it can usually be removed by laparoscopic surgery. Occasionally, an ovary containing a dermoid cyst becomes twisted on itself, causing severe pain. Surgical removal of the affected ovary, or oophorectomy, may be necessary if this happens.

Any cyst that is 6 centimeters in diameter—about the size of a peach—or larger in a premenopausal woman should be investigated immediately as a possible malignancy, says Rarick, as should a cyst of any kind in a woman who has completed menopause.

While some doctors will recommend surgical examination of a large ovarian cyst, many gynecologists will examine the mass through a laparoscope, says Rarick. "It's possible to use a needle to puncture the cyst or aspirate its contents. The cyst can even be removed through the laparoscopic incision."

Polycystic ovarian disease, also known as Stein-Leventhal syndrome, is a benign condition characterized by multiple small cysts on the ovaries. This disease has a distinct set of symptoms that may appear as early as adolescence and may include menstrual irregularity, abnormal growth of body hair, lack of breast development, obesity, and infertility. ■

—Eleanor Mayfield

Taxol's Long History

The healing properties of Taxol were known to at least one community long before Western medicine recognized the drug's potential.

According to an article in the Sept. 4, 1991, *Journal of the American Medical Association,* around the turn of the century, a British official in the Indian subcontinent noted that parts of the European yew, *Taxus baccata,* were used in an Indian clarified butter preparation for treating cancer.

It wasn't until 1962, however, that the U.S. Forest Service delivered crude bark extracts of the Pacific yew, *Taxus brevifola,* to the National Cancer Institute. A series of NCI experiments showed the extract was effective against several kinds of cancer in mice.

In 1971, researchers at the Research Triangle Institute in Durham, N.C., isolated Taxol from the extract, but interest in the compound waned until the mid-1970s. In 1979, a researcher at Albert Einstein College of Medicine in New York described how Taxol works to defeat cancer by inhibiting cell division.

Today, Taxol—alone or in combination with other drugs—is being studied for a wide variety of adult and childhood cancers. In July 1992, FDA authorized use of the drug for ovarian cancer under a "treatment IND." Treatment INDs permit earlier and wider access to experimental drugs by patients with life-threatening conditions for which there is no satisfactory treatment.

In December 1992, Taxol was approved for advanced disease unresponsive to other therapies. The drug was approved in a record five months. ■

—M.S.

Pacific yew

Pacific yew bark

used to treat ovarian cancer may also have neurologic effects, causing hearing loss, ringing in the ears, nerve damage, and numbness or tingling in the face, fingers and toes. There may also be kidney damage.

Most side effects are temporary, and sometimes dietary changes or medicines can ease the symptoms. There are several drugs approved for countering nausea and vomiting often associated with chemotherapy. They include Zofran (ondansetron hydrochloride), Reglan (metoclopramide), and Marinol (dronabinol).

Transfusions can correct red blood cell and platelet deficiencies. Hematopoietic growth factors such as G-CSF, approved in 1991, stimulate production of infection-fighting white blood cells. GM-CSF, which also received FDA approval in 1991 to increase white blood cell counts after bone marrow transplantation, is now being studied for its effectiveness in stimulating white cells after cancer chemotherapy. Among other drugs now under study for their ability to increase white cell counts, and perhaps platelets as well, are stem cell factor and PIXY 321. PIXY 321 is a genetically engineered product consisting of GM-CSF and another hematopoietic growth factor, interleukin-3.

When therapy is completed, the woman continues to have regular checkups that include pelvic examinations and laboratory tests to measure blood levels of tumor markers such as CA 125. The doctor may recommend a laparotomy or laparoscopy after completion of chemotherapy to inspect the abdomen and pelvis and take multiple tissue biopsies. This "second-look surgery" helps evaluate the effectiveness of chemotherapy and determine whether treatment should be continued or stopped. Often a laparotomy or laparoscopy has been done previously to diagnose ovarian cancer.

Attempts at Prevention

The Gilda Radner Familial Ovarian Cancer Registry advises women with two or more first- or second-degree relatives who have had the disease to have their ovaries removed via video laparoscopy as a precautionary measure by age 35, if they have completed their families. The registry also advises that there is a small increased risk (1.8 percent) of developing primary papillary cancer of the peritoneum for women who have had this prophylactic surgery. The registry also recommends that women with a family history of ovarian cancer receive genetic counseling, beginning in their early 20s, and have pelvic and abdominal examination, CA 125 testing, and transvaginal ultrasound every six months beginning in their early 30s.

Jessica Marsh, seven years after her diagnosis, is today free of cancer and feeling fine. "I've become a much more positive person since my cancer," she says. "Life is too short to worry about little things. If life deals me lemons, I'll make lemonade." ■

Marian Segal is a member of FDA's public affairs staff.

New Attitudes Towards Menopause

by Sheryl Weinstein

Imagine a cocktail party conversation in 1966 turning to menopause. It would have been as unlikely as a female high school student yearning to be a soccer star.

But times have changed. Just as participating in sports has now become significant to many young women, so has being open and even activist about menopause become equally important to their mothers.

The first women of the post-World War II generation known as baby boomers are now reaching the age of 50, one year away from the average age of menopause among U.S. women. By the end of this century, more women than ever before will be experiencing the sometimes uncomfortable symptoms that accompany the end of menstruation and natural childbearing capacity.

For many years, U.S. doctors knew little about and paid little attention to menopause. "About 20 years ago, medical attitudes started changing," says Isaac Schiff, M.D., chief of obstetrics and gynecology, Massachusetts General Hospital. "We Ob-Gyns used to think that when women reached age 50, they weren't interested in sex anymore. But studies in retirement communities showed otherwise. We also began to see an increase in the female life expectancy. When a woman reaches age 50, she typically has another 30 years to live. As physicians, we became interested not only in the quantity of her life, but the quality of it."

The pace of medical inquiry has accelerated over the last five years, as the first of the baby boomers turned 45 and started experiencing menopausal symptoms. "It's not uncommon to hear it discussed at cocktail parties," says Schiff. "This is a radical turn-around from the way the mothers of these women treated it. Speak to a 50-year-old woman and she'll say, my mother never discussed it with me."

With such thinking, a new attitude toward treatment and research has emerged, says Schiff. Until recently, there were few studies on menopause. One of the largest and potentially most fruitful is the Women's Health Initiative, sponsored by the National Institutes of Health, which will study 164,500 women of various racial and ethnic backgrounds across the United States. The scientific investigation, which will not be completed until 2005, is expected to find out whether a low-fat diet, hormone replacement therapy, calcium, and vitamin D might prevent heart disease, breast and colorectal cancers, bone fractures, and memory loss.

Hormone Replacement Therapy

As many as 15 to 25 percent of postmenopausal American women take hormone replacement therapy, according to an article in the January 1995 issue of the *Journal of Obstetrics and Gynecology* by Diane Wysowski, Ph.D., of the Food and Drug Administration, and colleagues. Women take estrogen to alleviate menopausal symptoms, especially hot flashes (sometimes called by doctors "hot flushes"), and also to protect bones.

Since the 1940s, FDA has approved many estrogen drugs to reduce menopausal symptoms. In the 1980s, FDA also began approving specific estrogen drugs to prevent osteoporosis (literally "porous bones," a condition in which bones break easily). The agency has approved four estrogen drugs—Premarin, Estraderm, Estrace, and Ogen—for long-term use to prevent osteoporosis. Other approved uses for estrogen drugs include the treatment of symptoms of vaginal atrophy, which may include itching, burning or dryness around the vagina, certain abnormal uterine bleeding conditions due to hormonal imbalance, and the comfort-promoting treatment of certain advanced cancers.

Many scientists believe that estrogen may fight heart disease by lowering harmful cholesterol (LDL), raising beneficial cholesterol (HDL), and strengthening the lining of the blood vessels, but this has not been clearly proven. Some research also suggests that estrogen may help prevent memory loss and Alzheimer's disease, but the scientific evidence remains speculative.

Women take estrogen to alleviate menopausal symptoms, especially hot flashes, and also to protect bones.

Nearly all the studies on heart disease and cognitive function have been retrospective or "look back" studies. The Women's Health Initiative Study will be prospective, that is, future-oriented, says Deborah Smith, M.D., a medical adviser in FDA's Office of Women's Health. Researchers will select a group of generally healthy women to treat and observe for a number of years to see if, and at what rate, they develop symptoms. Elements of the study will be scientifically controlled and data freshly recorded. Most important, treated and untreated women will be equally healthy at the start of the study. Retrospective studies depend on information sometimes clouded by time and memory loss, and women selected by their doctors for hormone replacement have usually been healthier than the women not so prescribed.

"The other important difference about the Women's Health Initiative is that it includes a clinical trial of estrogen," says Jacques Rossouw, the lead project officer for the study. "Participants will have an equal chance of being on either estrogen or a placebo, and any differences in their health at the study's end can be ascribed to the estrogen."

Risks of Estrogen Therapy

Estrogen is most commonly prescribed in pill form. It is also available in transdermal patches, which allow the drug to be slowly absorbed into the bloodstream, and in vaginal creams, which treat localized discomforts.

Estrogen replacement therapy is not risk-free. "There's been much experimental evidence and patient experience showing estrogen given alone can lead to endometrial cancer," says FDA's Smith. For that reason, a woman who still has a uterus is usually prescribed progestin in addition to estrogen. This significantly reduces the risk of abnormal changes in the uterine lining.

Endometrial cancer is not the only risk from estrogen use. Gallbladder disease is another. Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who don't use estrogens.

The drug's labeling also includes warning about abnormal blood clotting. Clots can cause a stroke, heart attack, or pulmonary embolus, any of which can be fatal.

Estrogen can produce uncomfortable side effects such as nausea and vomiting. It can enlarge breasts and make them tender. Women who use it can also retain excess fluid, which can aggravate conditions like asthma, epilepsy, migraines, and heart and kidney disease. A spotty darkening of the skin, particularly on the face, can occur.

For women who take progestin along with estrogen, menstrual-like bleeding and premenstrual symptoms often occur. Also under study is whether adding progestin counters the potential heart-

How Hot Flashes Happen

Hot flashes, the most common sign of approaching menopause, occur as the brain's hypothalamus adjusts to decreased estrogen production by the ovaries. The hypothalamus—some functions of which are manipulated by estrogen—regulates body temperature. When it senses lower estrogen levels, the hypothalamus responds by rapidly changing body temperature.

protective effects of estrogen.

It is not known whether estrogen use increases the risk of breast cancer, or what effect adding progestin has on this risk. In recent years, many studies on breast cancer and estrogen use have been conducted, with conflicting results, says Smith. Last year, following the publication in June 1995 of opposing views in two of the nation's most prestigious medical journals, the *New England Journal of Medicine* and the *Journal of the American Medical Association,* NIH scientists advised women to consult their "medical caregiver for advice that is based on the individual's own personal health profile." Physicians urge women who receive estrogen therapy to have regular breast examinations by a health professional, perform monthly self-exams, and have yearly mammograms starting at age 50.

Before Menopause

The medical term for the usually gradual period of change leading into natural menopause is "perimenopause." The two to three years following the last period are called the "climacteric." According to the American College of Obstetricians and Gynecologists, the average age of menopause in the United States is around age 51. But some women go through natural menopause as early as age 35, while others don't experience it until their late 50s. Menopause occurs at any age with surgical removal of the ovaries.

During perimenopause, estrogen production decreases and the ovaries stop producing eggs. As estrogen levels decline, certain signs may appear. The most common sign, the one that doctors sometimes call the "hallmark" of menopause, is the hot flash. A hot flash is a sudden rush of heat to the neck, face, and possibly other parts of the body that may last from 30 seconds to five minutes. Some women go from feeling hot to feeling cold. The hot flash may begin with a sudden tingling in the fingers, toes, cheeks, or ears.

Some people used to think the hot flash didn't exist, that it was "all in a woman's head," says Smith.

Ironically, it *is* in a woman's head—but it has a very real physical cause. The hot flash is an alteration in thermal stability, which is maintained by the hypothalamus, a brain region located above the pituitary gland on the brain's floor. The hypothalamus operates the body's temperature regulation system. Estrogen levels manipulate some functions of the hypothalamus. During menopause, as the ovaries produce less estrogen, the hypothalamus senses and responds to the lower estrogen levels by rapidly changing body temperature. The result may be a hot flash.

Perspiration, sometimes extreme sweating, can accompany hot flashes. Many of them typically occur in the middle of the night, waking the woman, who may have trouble falling back to sleep. How many women are affected by hot flashes has not been clearly determined, and the reported numbers depend in part on whether healthy populations or women in medical settings are surveyed. Some scientists say as few as 30 percent of women are afflicted by them; others believe the figure is much higher.

According to Morris Notelovitz, M.D., Ph.D., and colleagues in the text Menopause in *Midlife Health,* 85 percent of perimenopausal women experience hot flashes. Fifty-four percent of the women experience them in their climacteric years; 25 percent of these women experience hot flashes up to 10 years after the climacteric. About 10 percent of the women who continue to have hot flashes still have them for 10 years after the climacteric, according to Notelovitz.

Obese women are less likely to have hot flashes because they have more estrogen, which is converted from adrenal hormones by stored fat. Many women cope with hot flashes by trying to relax until the discomfort passes and by lowering the room temperature, dressing in light layers of clothing, avoiding spicy food, and cutting back on caffeine and alcohol.

Vaginal dryness is another symptom

of estrogen decrease and may lead to painful intercourse, vaginal infections, and urinary problems. Over-the-counter vaginal lubricants (Replens and others) may help. Prescription estrogen replacement creams are approved by FDA to relieve these symptoms.

Other symptoms attributed to menopause include difficulty concentrating, depression, headache, memory loss, a feeling of insects crawling across the skin, and lower backaches, which may be related to osteoporosis.

Barbara Sherwin, Ph.D., at the University of Toronto, and colleagues have been researching an association between menopause and memory loss, even Alzheimer's disease, and whether estrogen can halt these problems. Sally Shumaker, Ph.D., of the Bowman-Gray School of Medicine, North Carolina, is leading a $16 million study, the Women's Health Initiative Memory Study, to determine whether estrogen treatment affects a woman's risk of developing dementia after age 65. Wyeth-Ayerst Laboratories is funding the study.

Probably the disease with the strongest link to menopause is osteoporosis. Scientists believe women can help control bone loss with weight-bearing exercises, including walking, running or weightlifting. A low-fat diet, rich in calcium and vitamin D, is also believed to be important, as are cutting back on alcohol and stopping smoking. FDA has approved a nonhormonal drug to treat osteoporosis. (See "Boning Up on Osteoporosis" on page 21.)

Despite its sometimes annoying, peripheral problems, more than ever before menopause is now seen as a natural process, not a disease. "There's nothing embarrassing about it," says Schiff. "It's healthy. It's physiologic."

It is such new thinking that best explains why at cocktail parties and other places baby boomers congregate that menopause is a hot conversation topic. ■

Sheryl Weinstein is a writer in Livingston, N.J.

More Resources

American College of Obstetricians and Gynecologists (ACOG)
409 12th St., S.W., Washington, DC 20024-2188
(202) 484-3321
Send a self-addressed stamped envelope for three pamphlets about estrogen, osteoporosis and menopause.

American Menopause Foundation
P.O. Box 2013, New York, NY 10010
(212) 475-3107

North American Menopause Society (NAMS)
P.O. Box 94527, Cleveland, OH 44101
(216) 844-8748
http://www.menopause.org/
Answers written requests for information about menopause, and publishes a medical journal.

American Association of Retired Persons (AARP) Women's Initiative
601 East St., N.W., Washington, DC 20049
(1-800) 424-3410
Has a free fact sheet about hormone replacement therapy.

National Institute on Aging Information Center
P.O. Box 8057, Gaithersburg, MD 20898-8057
(1-800) 222-2225
Has free information on menopause, exercise and nutrition.

Planned Parenthood Federation of America, Inc.
810 Seventh Ave., New York, NY 10019
Has a booklet, "Menopause—Another Change in Life," available from the above address for $3. It can also be downloaded free through the World Wide Web at *http://www.ppfa.org/ppfa/menopub.html.*

The Power Surge Reading Room
An on-line menopause discussion area with an electronic newsletter. It can be accessed in its entirety through America Online with the keyword "Women," followed by the "well-being" icon, and in part through the World Wide Web at *http://members.aol.com/dearest/news.htm.*

Women's Health Initiative
Federal Building, Room 6A09
7550 Wisconsin Ave.
Bethesda, MD 20892-9112
(1-800) 54-WOMEN
Women interested in participating in the Women's Health Initiative can also find information at *http://odp.od.nih.gov/whi/* on the World Wide Web. ■

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