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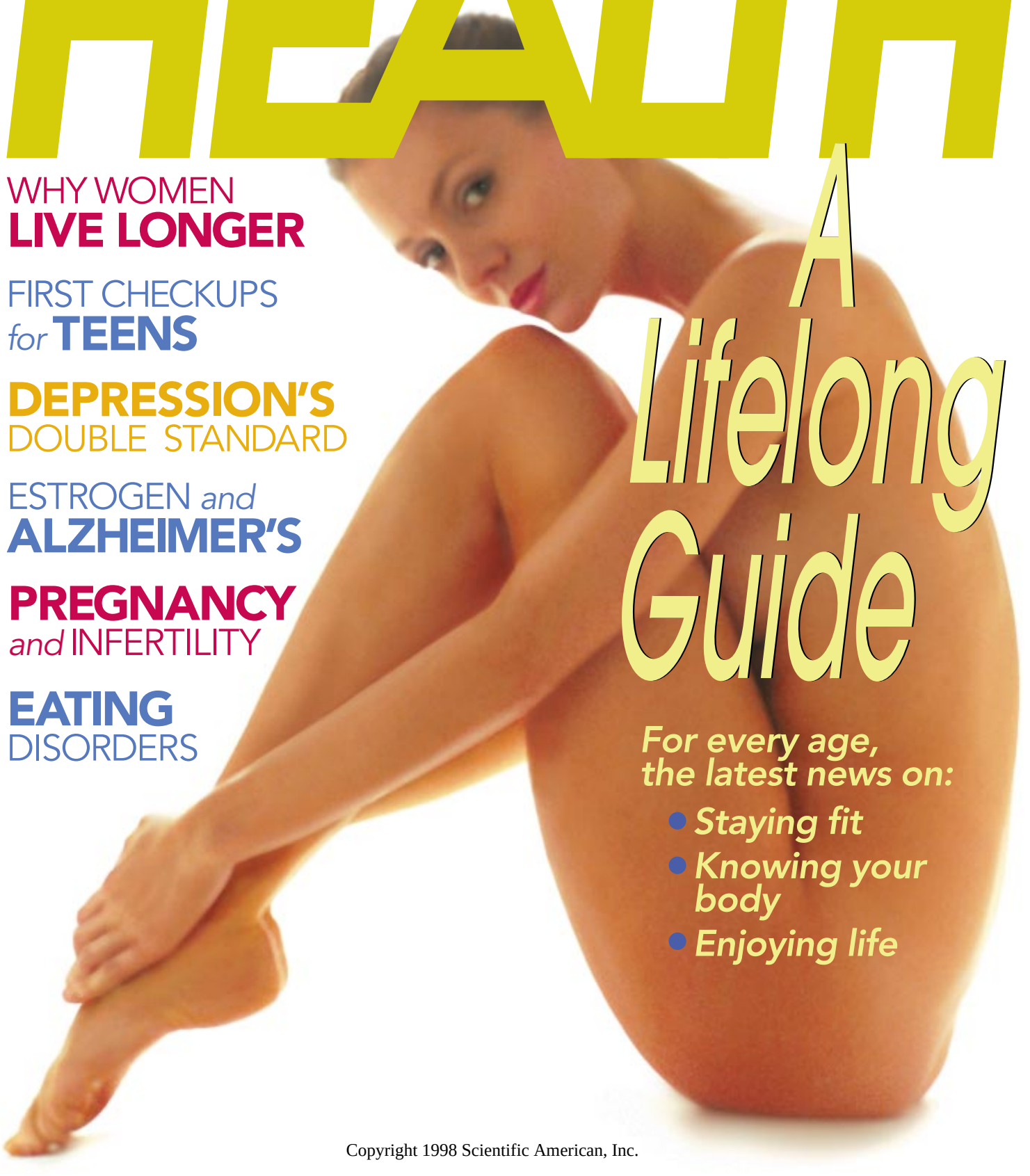
WOMEN'S HEALTH

A Lifelong Guide



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SCIENTIFIC AMERICAN PRESENTS WOMEN'S HEALTH *A Lifelong Guide* Quarterly Volume 9, Number 2

FROM THE EDITORS

Women: Healthy for a Lifetime

When women make up half the human race, does it really make sense to isolate "women's health" from health in general? Is what's left over automatically "men's health" by default, or is there a gender-neutral category, too? During the many months of preparation that went into this issue, the editors had plenty of time to ponder those questions. Comfortingly, we also had a steady stream of expert advice and evidence confirming our decision to focus on this important, timely topic.

Just as we were going to press, for example, headlines proclaimed "Women More Sensitive to Pain but Cope Better than Men." Researchers at Ohio University documented that although women's experience of pain was often worse, their emotional recovery was quicker. Then came news that women and men respond oppositely to some experimental painkillers. These discoveries underscored how subtle differences between the sexes can weigh powerfully on health and happiness.

JAMES LEYNSE SABA

Issue editors (from left to right): *Kristin Leutwyler, John Rennie, Carol Ezzell and Sasha Nemecek*

Viewed as a class, women run medical risks and face challenges to mental and physical well-being that men seldom, if ever, do. We've tried to make sure that any woman (or anyone who cares about women) looking for truthful answers about how to prevent or overcome those problems will find them in the pages ahead. To help readers find themselves and their health concerns more easily, we've segmented the contents by age—some advice is obviously more relevant at 16 than at 60. But don't feel excluded: most readers will find it makes sense to read every article for a lifetime perspective.

The guiding geniuses of this issue are editors Sasha Nemecek, Carol Ezzell and Kristin Leutwyler as well as photo editor Bridget Gerety, to whom all credit is due. My thanks also go out to the many experts whose help inspired and informed us at every step.

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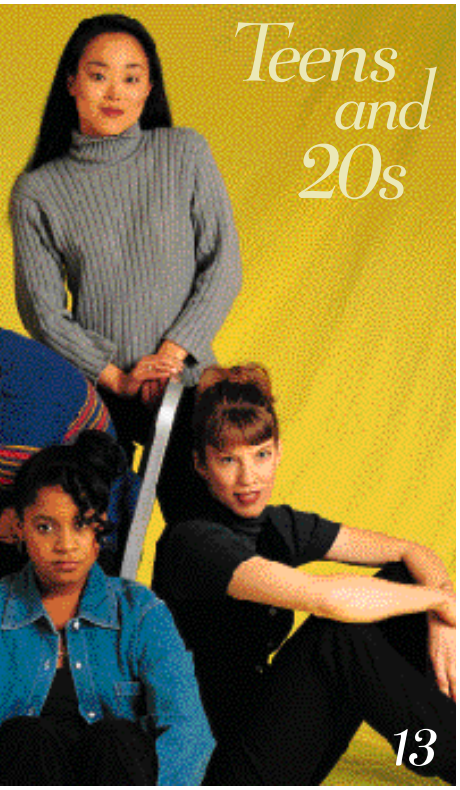
SCIENTIFIC AMERICAN, INC.
415 Madison Avenue • New York, NY 10017-1111
(212) 754-0550
PRINTED IN U.S.A.

SCIENTIFIC AMERICAN
PRESENTS
Summer 1998
Volume 9 Number 2



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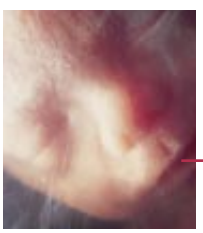


WOMEN'S HEALTH A Lifelong Guide

Q&A Questions and Answers

Cover photograph by Roy Volkmann

The Importance of Women's Health

Phyllis Greenberger, M.S.W.

Securing the right to vote, controlling fertility, earning (almost) equal pay for equal work—to this list of milestones for women, add one more: being included in all federally financed health studies. In 1993 Congress passed the equivalent of the Equal Rights Amendment for medical research: a law mandating that women be part of all studies that receive funding from the National Institutes of Health and that women be included in the final stages of all clinical trials of new drugs, unless there is some compelling medical reason they shouldn't be.

For many years, women were not systematically included in biomedical research and clinical trials, in part because of concern that if women became pregnant during the course of the study, the fetus might be harmed. Unfortunately, though, the policy meant that researchers simply did not know certain facts about women's health.

The 1993 law was a crucial landmark in the effort to look more closely at women's health—a movement that has been under way at least since the publication of the book *Our Bodies, Ourselves* in 1969. And as researchers have been asking more questions about women's health, they've been uncovering some fascinating and compelling answers. In this special issue of SCIENTIFIC AMERICAN, we hope to share with you some of these answers—from the experts who have been working to uncover them.

We've divided the issue by age groups to reflect the growing awareness that women's health is not just about the reproductive system but rather about a lifelong approach to staying healthy. We start off in the teen years, because it's really only after puberty that health concerns for boys and girls begin to diverge.

To introduce the issue, we asked ***EVELYN STRAUSS,*** special correspondent for SCIENTIFIC AMERICAN, to discuss priorities in women's health research and public policy with three women who are experts in these fields: ***PHYLLIS GREENBERGER, M.S.W.,*** executive director of the Society for the Advancement of Women's Health Research in Washington, D.C., an organization that has played a key role in altering the status of women's health research in this country and that continues to push for public policies that improve women's health; ***WANDA K. JONES, Dr.P.H.,*** deputy assistant secretary for health (women's health) in the Department of Health and Human Services; and ***VIVIAN W. PINN, M.D.,*** director of the Office of Research on Women's Health at the National Institutes of Health. *—The Editors*

PHOTOGRAPHS BY KATHERINE LAMBERT

Wanda K. Jones, Dr.P.H.

Vivian W. Pinn, M.D.

Q *What are the most significant health concerns facing women today?*

A **PINN:** We can consider the most important health concerns from two different perspectives: the leading causes of death for women and the major conditions or disorders that affect the health of women and the quality of their lives. One crucial consideration is to face the reality of the facts, rather than just common perceptions.

For example, many women (and even some of their physicians) still think of breast cancer as their leading cause of death, but that's not correct. Although breast cancer is the most common cancer in women and the leading cancer cause of death for women between the ages of 35 and 54, lung cancer has been the leading cancer cause of death for all women since 1985. And when women's entire life spans are considered, heart disease is the overall leading cause of death, followed by cancer, then stroke.

Most of the questions we receive at the Office of Research on Women's Health are about hormone replacement therapy (HRT) and menopause and about breast cancer. Women also ask about other conditions that affect them, such as urinary incontinence, aging, immune system diseases like lupus, and mental health disorders.

Traditionally, women's health concerns have been thought of as just associated with the reproductive system during childbearing years. But women's health has come to be seen in the context of an entire life span.

Some conditions are unique to women; these mostly relate to the reproductive system. Other conditions affect both men and women but may have different symptoms in the two sexes. As the concept of women's health has been expanded to the total body and health of women, we now have the deserved scientific attention focused on issues such as prevention, behavior and treatments that are of particular concern to women.

What is the Women's Health Initiative? What has it accomplished so far?

PINN: The Women's Health Initiative, or WHI, is a 15-year national study sponsored by the NIH to define better ways to prevent some of the major causes of death and disability in postmenopausal women: heart disease, cancers and osteoporotic fractures. The WHI, which will involve more than 167,000 women between the ages of 50 and 79, is one of the most definitive clinical trials of women's health ever undertaken in the U.S. This initiative will provide practical information to women and their physicians about the role of hormone replacement therapy in the prevention of heart disease and osteoporotic fractures; about dietary patterns in the prevention of heart disease, breast and colon cancer; and about the effects of calcium and vitamin D supplements on osteoporosis and colon cancer. This study should help resolve some of the questions related to the risks and benefits of long-term hormone replacement therapy. Another arm of this study is the community prevention study, a collaborative effort with the Centers for Disease Control and Prevention, to develop community-based public health intervention models that can achieve healthy behaviors in women ages 40 and older.

The WHI is a really powerful study because of the large numbers and diversity of women involved and the excitement of the women who are volunteers. There are 40 centers across the U.S., so we can take into account geographic factors as well as diversity in race and economic status in interpreting the findings to benefit all women in this country.

The study has succeeded in meeting its recruitment goals, including enrolling the largest number of minority women ever involved in a study funded by the NIH. When this study first started, many doubted that we would be able to get so many women to volunteer. But the women we've recruited have been very enthusiastic about the project and excited about being a part of a study that could lead to many answers that women have been seeking. This is significant because we're

getting away from attitudes that can make clinical research hard to do, when women do not understand the value of their participation. If we want more answers, women really have to volunteer for clinical trials such as the WHI. It's especially heartening that women are participating even though the results might not make a big difference for them but rather will benefit their daughters and granddaughters.

Has the recent increased focus on women's health changed how women take care of themselves and how research involving women is conducted?

GREENBERGER: I would hope so. We would be colossal failures if it hadn't. A lot of the knowledge up until now has been based on men, but women are demanding answers to their questions, and they want to know how research findings affect them. There are many more women in clinical trials now, and this is the only way we're going to get answers.

Because of demographics, the baby boom generation is going to be front and center in the public eye during the next few years, so issues relevant to these women are becoming very prominent. It's only recently that women have been spending almost a third of their lives after menopause—they realize they've got a lot of life left to live, and they want to remain healthy.

JONES: Unfortunately, we don't have a good indication that women are actually taking better care of themselves today. There's certainly much more information about health than there's ever been, but some of it conflicts—so the potential for confusion is higher than before, too. Today you hear coffee's okay, and tomorrow it's not. The six o'clock news will cover a study conducted on only 40 people, even if the results don't necessarily translate or have any relevance to the larger population. People don't have the ability to sift through this overload of sometimes contradictory information. It's worrisome to me that the public and the media want to put so much emphasis on every little new medical finding.

> *"WOMEN WANT TO KNOW HOW RESEARCH FINDINGS AFFECT THEM."*

One of the interesting things that will come out of the Women's Health Initiative is whether women's health behaviors changed during their involvement in the trial and whether they changed for better or worse. That might help us figure out ways to communicate important health issues to women.

PINN: I definitely think the increased focus on women's health has changed how women see their bodies and their health and has helped them to appreciate their own responsibilities for their health through their behavior. Many more women realize the role of nutrition and physical fitness in protecting their health, for instance. And these days, a postmenopausal woman isn't sitting in a rocking chair watching life go by. She's the CEO of a company or the winner of a tennis match at the sports club. Women are realizing that if they want to be active as mature women, they need to modify their behavior earlier in life. We're seeing issues like menopause and depression come out of the closet. Women are realizing that it's acceptable to ask questions and to seek medical help for conditions such as urinary incontinence, arthritis, depression and domestic violence, conditions that can occur in all cultures, at any socioeconomic status.

Research is designed to answer scientific questions. Women are realizing they should ask if they don't know the answer to questions about their health. And as they raise more questions about their health, their physicians and health care providers better realize the conditions for which research has not yet provided definitive answers: How will pregnancy or oral contraceptives affect my lupus? What is the real story about hormone replacement therapy? What are the medical alternatives to surgical hysterectomy? Why is there a higher mortality rate for some cancers in minority women? Why does heart disease occur later in life in women than in men and often lead to a higher mortality rate in women after a heart attack? Will the same interventions for the prevention of heart disease in men also prevent heart disease in women?

These kinds of questions reveal gaps in our scientific knowledge, and the way to get answers is through research. Previously, studies were done primarily on men, even when the conditions affected both women and men. Now we have a strengthened policy at the NIH that requires the inclusion of women in clinical studies, so women are participating in studies of the conditions that affect them.

What are the most important findings in women's health research from the past several years?

GREENBERGER: We're beginning to develop so-called designer estrogens for use in hormone replacement therapy—compounds that differentially affect estrogen receptors in different parts of the body, for example. We've discovered compounds that can selectively turn on and off the estrogen receptors in bone but not in the breast. This information can be used to develop compounds that can potentially eliminate some of the side effects of hormone treatment, such as the possible increased risk of breast cancer.

We're also beginning to see gender differences in terms of addiction, depression and cardiovascular disease as well as reaction to pain and anesthesia. We're recognizing that the circuitry of the male and female brains is different, which leads to questions about how different brain activity leads to depression, dyslexia and schizophrenia. With regard to pain, drugs known as kappa opioids work very well to kill pain after wisdom tooth extraction in women but hardly at all in men, suggesting that the neurology underlying pain pathways is different in men and women. Women have a far more powerful response to the drugs than men do, and the analgesic effects last considerably longer for women than for men.

Women smoke fewer and lighter-tar cigarettes than men do, but they have more cases and different kinds of lung cancer. It used to be thought that because more women are smoking, they're catching up to men in the incidence of lung cancer. But it's not just that women are smoking more; it's that they're more sensitive to whatever gives them lung cancer.

JONES: We're beginning to reap the benefits of research that was done several years ago. For example, we're seeing a decline in the number of HIV-infected newborns; several years ago researchers showed that treating infected women reduces the incidence of viral transmission to the fetus.

PINN: Many of the things we've learned confirm what we thought before. For example, sexual activity increases the risk of infection with human papillomavirus, and there's now a proven connection between the virus and cervical cancer. We've also learned that taking hormone replacement therapy

reduces risk factors for heart disease in women. The Women's Health Initiative will provide information about actual reduction in mortality. We're getting results suggesting that estrogen may play a role in preventing Alzheimer's disease in elderly women. We're gaining a lot more information about osteoporosis and how to prevent it through diet, calcium, physical activity and new medications.

Some of the most exciting new findings, however, are related to breast cancer. During the past several years, there have been breakthroughs in the recognition of the genetic mutations that may be responsible for breast cancer, and we are learning more about the detection of these mutations and how to manage them medically. The very recent and extremely important findings that tamoxifen, a drug that has been used to treat breast cancer, is also effective in reducing the chances of developing breast cancer offer new hope to women who fear breast cancer. Even as we learn more about the risks and benefits of tamoxifen, these results are a major step forward for women and their physicians in learning how to prevent this common cancer.

"WE NEED TO MAKE THE RESEARCH WE'VE ALREADY PAID FOR WORK FOR WOMEN. AND WE NEED TO FACILITATE WOMEN'S ACCESS TO HEALTH CARE."

What are the top questions concerning women's health that remain to be answered?

GREENBERGER: We need to understand why some diseases affect men and women differently and figure out what to do about it. For example, 80 percent of people with autoimmune disease are women. Why does depression affect women two to three times more than men? It's startling that we've gotten this far and not asked why—and what do we do about it.

JONES: A serious question that needs to be answered is, What are the unique features of disease in women that might require different or modified treatment strategies relative to men? In some instances, drugs are administered based on weight, but even so, a woman's metabolism might be different. Her hormones might have some modulating effect. I hear from women who are on medications for epilepsy or anxiety disorders that they notice a difference at various times of their menstrual cycles.

In terms of public health, it's important to know how men and women understand health messages—how they're likely to take information and figure out if it's relevant to them and then act on it. We also need more research to better understand how women use health care systems. Most women want to simplify their health care. It would be ideal if women could see their endocrinologist and their orthopedist in the same place on the same day. And for mothers, it would be good if the kids could go to their appointments at the same time as Mom—or if there were day care on the premises. We need to investigate these integrative approaches to providing health care.

The other big question is how research findings get translated into clinical practice. Why does it take 10 years for something to become standard practice? Right now in arthritis, too many people are being told that they should take a couple of anti-inflammatories and rest, and their arthritis will improve. But immobility lets the joints solidify. And this isn't just a women's research issue: arthritis affects more than 40 million people in the U.S., with about 60 percent of them women.

PINN: We need to understand not only the genetic and molecular basis of disease but also whether—and why—some of these conditions affect women and men differently. We need to know more about when and why there may be gender differences in the effects of drugs or other therapies. We need to understand the role of female sex hormones and their effects on health and disease.

In addition to comparing women with men, we need to look at other factors that result in differences in health status and outcome among various populations of women. Educational level, genetic inheritance, biological mechanisms, the environment, ethnicity, cultural practices and occupation are such factors that must be considered in addition to women's access to health care. And as we learn more about risk factors for disease, we must learn how to modify unhealthy behavior in women, such as smoking and poor dietary habits. Then, I hope, we can decrease the incidence of many health problems as well as learn how to detect them earlier with better interventions to prevent or cure diseases.

Women's health groups have become more politically active over the past few years. Has that paid off? If so, how?

GREENBERGER: The efforts of our group, the breast cancer groups and many others are definitely paying off in both the private and public sectors. We've gotten more funding for women's health research. Pharmaceutical companies are churning out many more products—particularly for women or for diseases that women suffer from disproportionately as compared with men. Plus we've been instrumental in setting up offices of women's health in several federal agencies. There's been a lot of recent legislation for funding research into diagnosis and treatment programs directed at women.

JONES: Advocacy by the National Breast Cancer Coalition and other groups—such as the Susan G. Komen Breast Cancer Foundation, the Y-ME National Breast Cancer Organization and the National Alliance of Breast Cancer Organizations—to increase breast cancer research has had a big impact. It's increased the budgetary commitment to breast cancer over the past five years and heightened women's awareness of the disease. That's great, but we also need to make the research we've already paid for work for women. The communication issues are critical. We also need to facilitate women's access to health care.

PINN: This attention from women's health advocacy groups and women's health professionals has raised women's health issues to a level where the scientific, medical, legislative and public-policy communities have gained an increased consciousness of our gaps in knowledge and have increasingly responded in effective and positive ways. We also have much more responsible and extensive media coverage of women's health issues, which assists in getting the messages out to individual women and their families. They're putting forward not just sensational sound bites but also the real controversies that exist within the health research community. That's important because we must get this information back to women and their health care providers, so that our expanded knowledge about women's health can make a difference in the quality of women's lives. SA

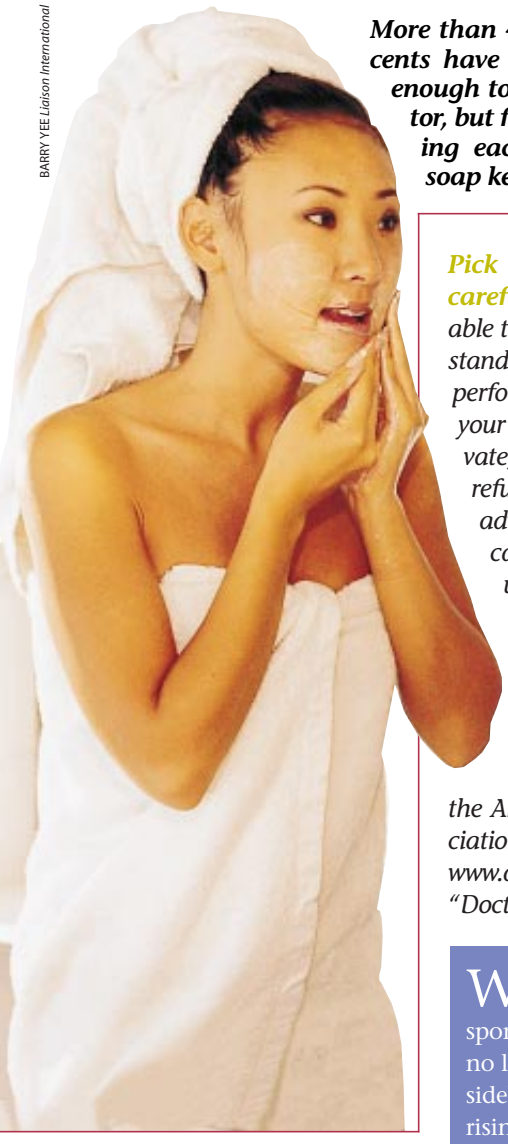
PHOTOGRAPH BY JAYNE WEXLER; HAIR AND MAKEUP BY LANA GERSMAN; BACKDROPS BY CHARLES BRODERSON

Roughly 36 million women in the U.S. are in their teens and 20s, a time in life when many health habits, such as eating a balanced diet and exercising regularly, are formed.

Teens and 20s

FACT SHEET

What women in their teens and 20s need to know



BARRY YEE *Liaison International*

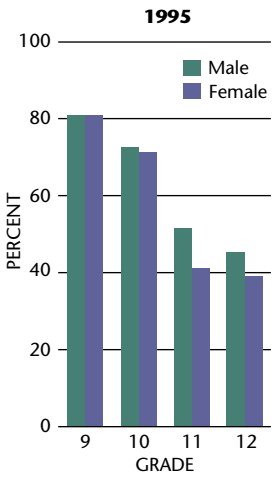
More than 40 percent of adolescents have acne that is severe enough to be treated by a doctor, but for most people, washing each day with a mild soap keeps acne tolerable.

Pick your gynecologist carefully. *You should be able to ask questions, understand what tests are being performed and why, keep your medical records private, and retain the right to refuse any treatment or advice. Do some research: call a local college or university clinic and ask for recommendations; talk to your mom and friends about their favorite gynecologists. You can check your doctor's background on the American Medical Association's Web site at http://www.ama-assn.org/ using the "Doctor Finder."*

In 1995 nearly 7 percent of young women ages 15 to 19 tested for **CHLAMYDIA** at family-planning clinics were infected with this sexually transmitted disease that can lead to permanent infertility. Among women ages 20 to 24, the rate was 4 percent. Chlamydia can be treated with one dose of the right antibiotic.

When it comes to sports, young women are no longer sitting on the sidelines. And with the rising numbers of female athletes, doctors are seeing more **knee injuries**. Women are two to eight times more likely than men to develop a tear in the anterior cruciate ligament of the knee. Researchers at the University of Michigan Medical Center and the Cincinnati Sports Medicine Clinic found that these injuries often occur during ovulation—suggesting that estrogen may play a role.

U.S. STUDENTS ENROLLED IN PHYSICAL EDUCATION



SOURCE: Youth Risk Behavior Survey

According to the 1997 U.S. *Shape of the Nation* report, 47 states have mandates for physical education. Illinois is the only state that requires daily **physical education** for all students, kindergarten through 12th grade; Alabama and Washington require daily physical education for all students through eighth grade. The majority of high school students take physical education for only one year between ninth and 12th grades.

The Centers for Disease Control and Prevention (CDC) reports that although **smoking rates among teens** dropped during the past 20 years, over the past five years they have begun to rise. In 1992 only 17 percent of girls in their senior year of high school said they smoked. By 1997 the number of high school girls who smoked was 35 percent. The CDC has projected that more than five million young people alive today will die prematurely from a smoking-related disease.

CHECKUP

Essential medical exams for women in their teens and 20s

PELVIC EXAM AND PAP TEST

When you turn 18 or become sexually active, it's time to schedule a pelvic examination and Pap test. Nobody loves going in for these, but remember, neither should be painful, and they could save your life.

During the exam, your doctor will first look at your external genitalia for signs of irritation or disease. Then she (or he) will use a tool called a speculum to separate your vaginal walls. Next, your doctor will perform a Pap test to check your cervix for abnormal cells that could indicate a precancerous condition. She will scrape cells from your cervix and cervical canal in a quick and painless procedure. (If anything ever hurts during the exam, tell your doctor immediately.) The Pap test is particularly important to have if you are or have been sexually active: it can help diagnose human papillomavirus (HPV), a common sexually transmitted disease that can cause cervical cancer.

After removing the speculum, your doctor will feel your ovaries, uterus and fallopian tubes to make sure they are healthy. She may then perform a rectal exam to check for abnormalities in the wall separating the rectum and vagina.

Most doctors recommend a pelvic exam once a year, and the American Cancer Society suggests a Pap test be performed during your first three pelvic exams. If the results are normal, ask your doctor how often you should schedule future Pap tests.

COST: Pelvic exam $40–$100; Pap test $20–$60. Usually covered by insurance.

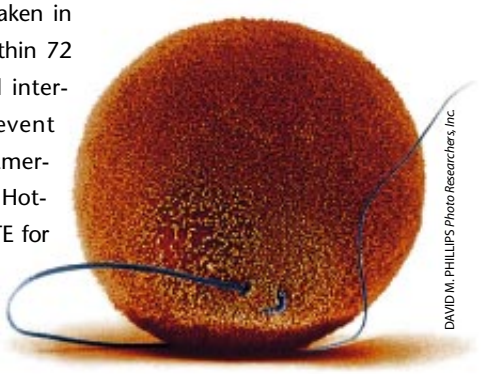
BETH PHILLIPS

In the 1970s **birth-control pills** were thought to increase your risk of a heart attack or stroke by causing blood clots, but modern pills pack lower doses of synthetic hormones and are considered highly effective and safe. Yet the long-term effects are largely a mystery, and there may still be some risk involved. Schedule a checkup within three months of taking your first prescription. Your doctor needs to monitor your blood pressure and watch for side effects such as headaches, hair growth and spotty menstrual bleeding. You should also ask your doctor whether other forms of hormonal contraceptives—implants or injections—are right for you.

66% of sexually transmitted diseases occur in people under age 25. (Institute of Medicine, 1997)

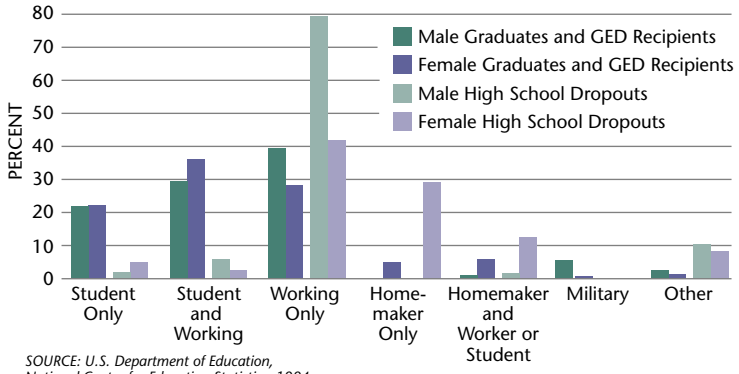
Nearly four in 10 teen pregnancies end in abortion. In 1997 the Food and Drug Administration confirmed that six brands of oral contraceptives are safe and effective as **emergency contraception.** If the pills are taken in the proper dosage within 72 hours of unprotected intercourse, they can prevent pregnancy. Call the Emergency Contraception Hotline at 888-NOT-2-LATE for more information.

48% of women between the ages of 15 and 44 have had at least one unplanned pregnancy. (Alan Guttmacher Institute, 1998)



DAVID M. PHILLIPS *Photo Researchers, Inc.*

LIFE AFTER HIGH SCHOOL



SOURCE: U.S. Department of Education, National Center for Education Statistics, 1994

BLOOD PRESSURE TEST

This is as quick and easy as a test gets: your blood pressure should be checked every time you go to the doctor, without your even having to ask. Your blood pressure should be below 140/90. Make sure you are tested annually if you're African-American, are overweight or have a family history of high blood pressure. The American Heart Association recommends that everyone have a blood pressure test once every two years.
COST: Included in a routine visit to the doctor and free at many pharmacies.

SKIN EXAM

Have a doctor examine your skin for irregular moles or skin color. Your doctor may suggest you see a dermatologist if he finds anything suspicious. The American Cancer Society recommends an exam once every three years between the ages of 20 and 40. Call 800-ACS-2345 to learn more about skin cancer.
COST: Included in a routine visit to the doctor.

CHOLESTEROL TEST

You might not be thinking about cholesterol yet, but high levels of cholesterol increase your risk of heart disease, so find out what your level is now. The National Cholesterol Education Program—run by the National Heart, Lung and Blood Institute (NHLBI)—recommends testing once every five years for people 20 years of age and older. Your primary care doctor will take a blood sample for analysis and may suggest a low-fat diet and exercise if your cholesterol level is too high.

To learn more about cholesterol and your heart, check out the NHLBI site at http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm on the World Wide Web.
COST: $20–$35

BREAST EXAM

It's not too soon to be aware of breast cancer. The American Cancer Society recommends that you examine your breasts for unusual lumps or bumps once a month right after your period ends and have your gynecologist examine your breasts every three years once you turn 20. To learn more about breast self-exams, see http://www.plannedparenthood.org/bc-and-wh/womens-health/exam/default.htm#breastexam on the World Wide Web. If there is a history of breast cancer in your family, ask your doctor about when to start having mammograms.
COST: Included in a routine visit to the doctor; often accompanies a pelvic exam.

TESTING FOR STDs

Ask your physician about being tested for the human immunodeficiency virus (HIV) as well as other common sexually transmitted diseases (STDs), such as chlamydia, herpes, gonorrhea and hepatitis B.

Be aware, however, that the results of the HIV test will go on your medical records permanently if it is not done anonymously; the outcome of this test could affect your ability to obtain insurance coverage later on. To find anonymous testing sites for HIV, call the Centers for Disease Control and Prevention's National HIV and AIDS Hotline at 800-342-2437. There's also a hotline specifically for other STDs: the National STD Hotline at 800-227-8922.
COST: $30–$100

DENTAL EXAM

Visit the dentist regularly to have your teeth cleaned and examined for cavities.
COST: $60–$200

COMPILED BY STEPHANIE J. ARTHUR AND KRISTA MCKINSEY; GRAPHS BY LAURIE GRACE

ABRAHAM MENASHE

Dying to Be Thin

Eating disorders cripple—literally—millions of young women, in large part because treatments are not always effective or accessible

by Kristin Leutwyler,
staff writer

I don't own a scale. I don't trust myself to have one in the house—maybe in the same way that recovered alcoholics rightfully clear their cabinets of cold medicines and mouthwash. At 5'7", I know that I usually weigh 118 pounds, and I know that is considered normal for my frame. But 13 years ago, when I was 15 years old and the same height, I weighed 67 pounds, and I thought I was grossly, repulsively obese.

My own bout with anorexia nervosa—the eating disorder that made me starve myself into malnutrition—was severe but short-lived. I had a wonderful physician who worked hard to earn my trust and safeguard my health. And I had one great friend who slowly, over many months, proved to me that one ice cream cone wouldn't make me fat nor would being fat make me unlovable. A year later I was back up to 95 pounds. I was still scrawny, but at least I knew it.

I was—am—lucky. Eating disorders are often chronic and startlingly common. One percent of all teenage girls suffer from anorexia nervosa at some point. Two to 3 percent develop bulimia nervosa, a condition in which sufferers consume large amounts of food only to then "purge" away the excess calories by making themselves vomit, by abusing laxatives and diuretics, or by exercising obsessively. And binge eaters—who overeat until they are uncomfortably full—make up another 2 percent of the population.

Anorexia nervosa affects many young women, such as this patient in the eating disorders clinic at the New York State Psychiatric Institute, a part of Columbia-Presbyterian Medical Center.

In addition to the mental pain these illnesses cause sufferers and their families and friends, they also have devastating physical consequences. In the most serious cases, binge eating can rupture the stomach or esophagus. Purging can flush the body of vital minerals, causing cardiac arrest. Self-starvation can also lead to heart failure. Among anorexics, who undergo by far the worst complications, the mortality rate after 10 years is 7.7 percent, reports Katherine A. Halmi, a professor of psychiatry at Cornell University and director of the Eating Disorders Clinic at New York Hospital in Westchester. After 30 years of struggling with the condition, one fifth die.

Because studies clearly show that people who recover sooner are less likely to relapse, the push continues to discover better treatments. Eating disorders are exceedingly complex diseases, brought on by a mix of environmental, social and biological factors. But in recent years, scientists have made some small advances. Various forms of therapy are proving beneficial, and some medications—particularly a class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs)—are helping certain patients. "SSRIs are not wonder drugs for eating disorders," says Robert I. Berkowitz of the University of Pennsylvania. "But treatments have become more successful, and so we're feeling hopeful, even though we have a long way to go to understand these diseases."

Weighing the Risks

When I began working on this article, I phoned my former physician, a specialist in adolescent medicine, and I was a little surprised that she remembered my name but not my diagnosis. In all fairness, my illness was a textbook case. I had faced many common risk factors, starting with a "fat list" on the bulletin board at my ballet school. The list named girls who needed to lose weight and by how much. I was never on it. But the possibility filled me with so much dread that at the

start of the summer, I decided I had to get into better shape. I did sit-ups and ran every day before and after ballet classes. I stopped eating sweets, fats and meat. And when I turned 15 in September, I was as lean and strong as I've ever been.

Scientists know that environment contributes heavily to the development of eating disorders. Many anorexic and bulimic women are involved in ballet, modeling or some other activity that values low body weight. Men with eating disorders often practice sports that emphasize dieting and fasting, such as wrestling and track. And waiflike figures in fashion and the media clearly hold considerable sway. "The cultural ideal for beauty for women has become increasingly thin over the years," Berkowitz notes. In keeping, among the millions now affected by eating disorders every year, more than 90 percent are female.

Like me, most young women first develop an eating disorder as they near puberty. "Girls start to plump up at puberty," Estherann M. Grace of Children's Hospital in Boston says. "And this is also when they start looking at magazines and thinking, 'What's wrong with me?' " Recognizing that anorexia nervosa often arises as girls begin to mature physically, psychiatrists recently revised the diagnostic standards. "It used to be that one of the criteria was that you had to have missed a period or suffered from amenorrhea for three months," says Marcie B. Schneider of North Shore University Hospital. "And so we missed all those kids with eating disorders who had not yet reached puberty or had delayed it." Now the criteria include a failure to meet expected growth stages, and more 10-, 11- and 12-year-olds are being diagnosed.

Puberty is a stressful time—and stressful events typically precede the onset of psychiatric conditions, including eating disorders. Maybe I would have stopped dieting had my parents not separated in the summer, or my grandmother had not died that fall, or I hadn't spent my entire winter vacation dancing 30-odd performances of the *Nutcracker*. Maybe. I do know that as my life spun out of control around me, my diet became the one thing I felt I could still rein in. "Anorexics are terribly fearful of a loss of control," Grace says, "and eating gives them one area in which they feel they have it."

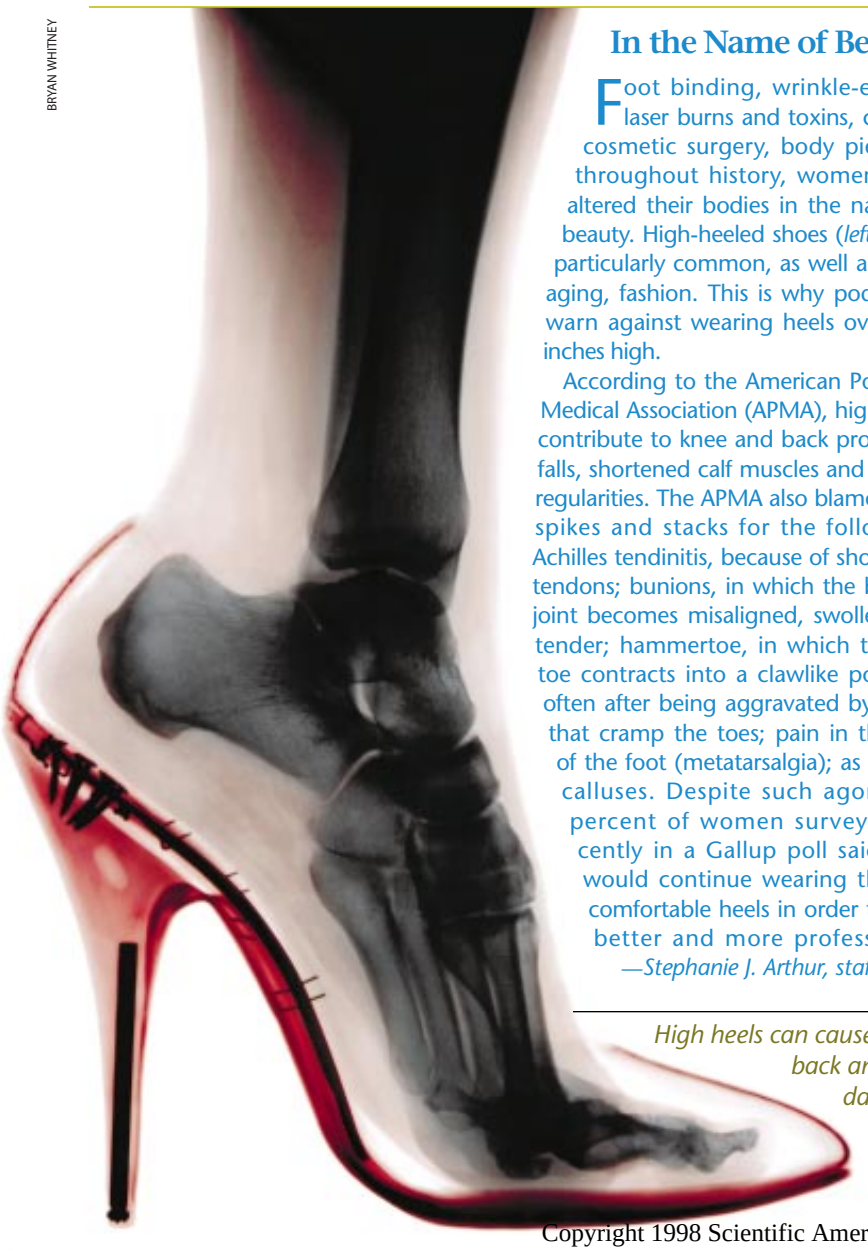
Most people under stress will overeat or undereat, Grace adds, but biology and personality types make some more vulnerable to extremes. Anorexics tend to be good students, dedicated athletes and perfectionists—and so it makes some sense that in dieting, too, they are highly disciplined. In contrast, bulimics and binge eaters are typically outgoing and adventurous, prone to impulsive behaviors. And all three illnesses frequently arise in conjunction with depression, anxiety and obsessive-compulsive disorder—conditions that tend to run in families and are related to malfunctions in the system regulating the neurotransmitter serotonin.

I most definitely became obsessed. I read gourmet magazines cover to cover, trying to imagine the taste of foods I would not let myself have—ever. I cut my calories back to 800 a day. I counted them down to the singles in a diet soda. I measured and weighed my food to make my tally more accurate. And I ate everything I dished, to make sure I knew the precise number of calories I had eaten. By November, none of my clothes fit. When I sat, I got bruises where my hip bones jutted out in the back. My hair thinned, and my nails became brittle. I was continuously exhausted, incredibly depressed and had no intention of quitting. It felt like a success.

Sitting Down for Treatment

The first barrier to treating eating disorders is getting people to admit that they have one. Because bulimics are often a normal weight and hide their strange eating rituals, they can be very hard to identify. Similarly, binge eaters are extremely secretive about their practices. And even though seriously ill anorexics are quite noticeably emaciated, they are the least willing of all patients with eating disorders to get help. "Anorectics are not motivated for treatment in the same way as bulimics are," Halmi comments. "Because anorexia gives patients a sense

BRYAN WHITNEY



In the Name of Beauty

Foot binding, wrinkle-erasing laser burns and toxins, corsets, cosmetic surgery, body piercing: throughout history, women have altered their bodies in the name of beauty. High-heeled shoes (*left*) are a particularly common, as well as damaging, fashion. This is why podiatrists warn against wearing heels over two inches high.

According to the American Podiatric Medical Association (APMA), high heels contribute to knee and back problems, falls, shortened calf muscles and gait irregularities. The APMA also blames high spikes and stacks for the following: Achilles tendinitis, because of shortened tendons; bunions, in which the big toe joint becomes misaligned, swollen and tender; hammertoe, in which the big toe contracts into a clawlike position, often after being aggravated by shoes that cramp the toes; pain in the ball of the foot (metatarsalgia); as well as calluses. Despite such agony, 37 percent of women surveyed recently in a Gallup poll said they would continue wearing the uncomfortable heels in order to look better and more professional.

—Stephanie J. Arthur, staff writer

High heels can cause knee, back and foot damage.

of control, it is seen as a positive thing in their lives, and they're terrified to give that up."

I certainly was—and a large part of getting better involved changing that way of thinking. To that end, cognitive behavioral therapy (CBT) has had fair success in treating people with anorexia, bulimia and binge eating disorder. "There are three main components," explains Halmi, who views CBT as one of the most effective treatments. Patients keep diaries of what they eat, how they feel when they eat and what events, if any, prompt them to eat. I used to feel guilty before meals and would ask my mother for permission before I ate. She never would have denied me, but asking somehow lessened my guilt.

CBT also helps patients identify flawed perceptions (such as thinking they are fat) and, with the aid of a therapist, list evidence for and against these ideas and then try to correct them. This process let me eventually see the lack of reason in my belief that, say, a single cookie would lure me into a lifetime bender of reckless eating and obesity. And CBT patients work through strategies for handling situations that reinforce their abnormal perceptions. I got rid of my scale and avoided mirrors.

Working in collaboration with researchers at Stanford University, the University of Minnesota and the University of North Dakota, Halmi is now comparing relapse rates in anorexics who have been randomly assigned to treatment with CBT or the SSRI drug Prozac, or a combination of both. Unfortunately, the dropout rate has been high. But earlier evidence has suggested that Prozac—which had not yet been approved when I was sick—may benefit some patients, helping them to at least stop losing weight. "Essentially every young woman with anorexia is also dealing with depression, and so SSRIs help alleviate some of the somatic symptoms associated with that," Grace says.

Not everyone believes SSRIs do much for anorexics, particularly those who are not desperately ill. But SSRIs have proved effective in people with bulimia. In conjunction with James Mitchell, director of neuroscience at the University of North Dakota, and Scott J. Crow, professor of psychiatry at the University of Minnesota, Halmi has just completed collecting data on 100 bulimics who received cognitive behavioral therapy for four months. Those who still did not improve underwent further therapy and drug treatment with Prozac. "When it comes to bulimia," Berkowitz tells me, "it is clear that both psychotherapy and pharmacology are helpful."

Swallowing the Truth

New treatments for eating disorders could benefit millions of adolescents—if they can get them. Most face a greater challenge getting help today than I did 13 years ago. "One of the big topics now is how to survive in this era of managed care," Schneider tells me. "You have to be at death's door to get into a psychiatric hospital," Berkowitz says, "and once a patient is stabilized, the reimbursements often stop. This is not an inexpensive disease to have." I went through a year of weekly therapy before I reached a stable, if not wholly healthy, weight. In comparison, Berkowitz notes that the insurance policies he has encountered recently often pay for only 20 sessions, with the patient responsible for a 50 percent co-payment.

"It's absolutely sinful," Halmi says. "It is a disaster for eating-disorder patients, particularly anorexics." She points out that relapse rates are much lower in adolescents who receive treatment long enough to get back up to 90 percent of their ideal weight; those who gain less typically fare worse. But insurance rarely lasts long enough. "It used to be you could hospitalize a kid for three or four months," Schneider says. "Now you can at most get a month or so, and it's on a case-by-case basis. You're fighting with the insurance company every three days." The fact that it may be cheaper to treat these patients right the first time seems to make little difference to insurance companies, she adds: "Their attitude is that these kids will probably have a different carrier down the road."

Down the road, the consequences of inadequate treatment are chilling. Debra K. Katzman of the Hospital for Sick Children in Toronto recently took magnetic resonance imaging (MRI) scans of young women with anorexia nervosa before and after recovery and found that the volume of cerebral gray matter in their brains seemed to have decreased—permanently. "The health of these kids does rapidly improve when they gain back some weight," Schneider says, "but the changes on the MRIs do not appear to go away."

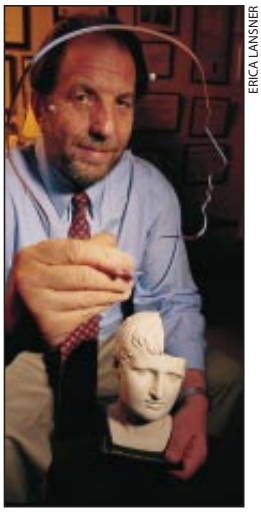
In addition, those who do not receive sufficient nutrition during their teen years seriously damage their skeletal growth. "The bones are completed in the second decade, right when this disease hits, so it sets people up for long-term problems," Grace asserts. These problems range from frequent fractures to thinning bones and premature osteoporosis. "I talked to one girl today who is 16. She hasn't been underweight for that long, but already she is lacking 25 percent of the bone density normal for kids her age," Schneider says. "And I have to explain to her why she has to do what no inch in her wants to—eat—so that she won't be in a wheelchair at age 50."

Because drugs used to treat bone loss in adults do nothing in teens, researchers are looking for ways to remedy this particular symptom. "[Loss of bone is] related to their not menstruating and not having estrogen," Grace explains. "But whereas estrogen does protect older women against bone loss, it doesn't seem to help younger ones." She and a coworker are now testing the protective effects of another hormone in young girls. Halmi also emphasizes that estrogen treatment for patients with eating disorders is a waste of time. Instead "you want to get them back up to a normal weight," she states, "and let the body start building bone itself."

All of which brings us back to the concept of normal weight—something many women simply don't want to be. A recent study found that even centerfold models felt the need to lie about their heights and weights. Christopher P. Szabo of the Tara Hospital in Johannesburg reviewed the reported measurements of women in South African editions of *Playboy* between February 1994 and February 1995 and calculated their apparent body mass indices. Even though these models all looked healthy, 72 percent had claimed heights and weights that gave them a body mass index below 18—the medical cutoff for malnourishment. "Maybe 5 percent of the population could achieve an 'ideal' figure, with surgical help," Grace jokes. "I'm sorry, but Barbie couldn't stand upright if she weren't plastic."

I remember all too well thinking that I would look fat at a normal weight. Sometimes I still do worry that I look fat. But I take my perceptions with a grain of salt. After all, I haven't exactly proved myself to be a good judge in that regard. Somehow I've come to a point where I don't need to measure my self-worth in pounds—or the lack thereof—provided I'm happy and well. I gave up a lot—ballet, friendships, a sense of community and security. But in return, I got my health back. SA

Q&A Migraine Headaches


ERICA LANSNER

Fred D. Sheftell, M.D.

Some 20 million women in the U.S.—nearly one in seven—suffer from migraines, making this ailment one of the most common to strike women. The majority of migraine patients have their first attack before age 30. ***MIA SCHMIEDESKAMP,*** *special correspondent for* SCIENTIFIC AMERICAN, *talks about migraine with* ***FRED D. SHEFTELL, M.D.,*** *cofounder of the New England Center for Headache and president of the American Council for Headache Education.*

Q *How would you describe a migraine headache?*

A A typical migraine is characterized by throbbing pain on one side of the head, nausea, sensitivity to light and sound and, in some cases, visual or other sensory disturbances. Surprisingly, 60 percent of sufferers have never been diagnosed. Indeed, many U.S. doctors leave their training woefully unprepared to recognize and treat migraine: on average, they receive just one or two hours of instruction on common headache ailments.

What happens during a migraine? Who gets them?

The pain of a migraine results in part from dilation of blood vessels and irritation of nerves in the covering of the brain. This abnormality stems from the disrupted regulation of various neurochemicals, including serotonin, which can work to narrow blood vessels. We know, for example, that the female sex hormone estrogen is involved in regulating these chemicals and in priming blood vessels for the action of serotonin. When estrogen drops, a migraine can follow. Depression is also mediated by these same types of chemicals. In fact, migraine and depression often occur in the same people. In many cases, migraine appears to be hereditary. More than 70 percent of people with migraine have a close relative who also suffers from the disorder.

Does migraine affect women differently than men?

Migraine is not an equal-opportunity disorder. Although in childhood the prevalence of migraine in girls and boys is about equal, after puberty the ratio of female to male sufferers leaps to nearly three to one. The female hormonal cycle seems to be responsible for much of this difference.

Women often experience worsened migraines during times of falling (but not rising) estrogen levels, which occur with menstruation, ovulation and the onset of menopause. Sixty percent of women with migraine report headaches with their periods.

We know that migraines often worsen in women using cyclical hormone therapies—such as oral contraceptives—which subject the body each month to fluctuating levels of hormones. Unfortunately, most gynecologists do not consider a woman's history of migraine when prescribing hormones. We generally do not prescribe oral contraceptives for our migraine patients. And for menopausal and postmenopausal women with migraine, we suggest steady, daily doses of hormones.

Can migraines be prevented?

Migraine headaches can be triggered by a number of factors over which sufferers can exercise some control. The top two dietary triggers are alcohol, especially red wine and beer, and the artificial sweetener aspartame. We also look at chocolate, aged cheeses, nitrites, caffeine and MSG as potential dietary factors.

Sensory stimuli, including bright or flickering lights, computer screens and odors such as perfume and cigarette smoke can precipitate migraine headaches. Stress and changes in sleep patterns also exacerbate the disorder.

Finally, I cannot say enough about the importance of regular exercise. Exercise reduces stress, increases circulation and produces painkilling chemicals called endorphins. The more women do in terms of improving their daily habits—getting proper nutrition, exercise, consistent sleep—the less medication they are going to need in the long term.

What are some of the most useful migraine drugs?

The introduction of Imitrex in 1993 was probably the major innovation in migraine therapy of this century. This drug was designed to mimic serotonin—it reduces dilation of blood vessels. Attacks that might last one or two days can be aborted in one or two hours. The past eight months have seen the introduction of at least five new drug options for migraine. These include Imitrex and Migranal nasal sprays, which can be taken despite nausea and vomiting, drugs with high tolerability (Amerge) and very consistent effects (Zomig), and an over-the-counter analgesic marketed specifically for migraine (Excedrin).

For women who cannot take Imitrex or similar drugs because of risk of stroke, for example, we can prescribe effective painkillers. We also use preventive medications, including antidepressants, which raise the level of serotonin, and beta blockers, which are used more commonly against high blood pressure. With the array of drugs now available, the vast majority of women with migraine should benefit from treatment.

One of the biggest problems we still face is that many women do not see any doctor besides their gynecologist. Women should be particularly cautious about medicating themselves. Daily use of analgesics can lead to chronic, so-called rebound headaches. We find that when we get patients off daily analgesics, 80 percent of them greatly improve. Women should not believe the myth that they simply have to learn to live with migraines. "Migraine" is not just another word for headache; it is a debilitating disorder that can have a profound impact on a woman's ability to function at work, home and play. SA

For more information, contact the American Council for Headache Education at http://www.achenet.org on the World Wide Web or call 800-255-ACHE.

Help for Victims of Rape

J. W. STEWART

Confronting painful memories of rape can help victims cope with the trauma

by Denise Grady, *special correspondent*

Years after being raped by three men at the age of 16, a 35-year-old woman was still disturbed by nightmares, anxiety, frightening memories and vivid flashbacks that made her feel as if she were reliving the attack. Worn out from useless efforts to keep the crime out of her mind, she sought help four years ago at the Center for the Treatment and Study of Anxiety at Allegheny University of the Health Sciences. There, director Edna B. Foa, professor of psychiatry, has developed a novel method for treating rape victims, called exposure therapy, that has shown promising results.

The woman's symptoms were the hallmarks of post-traumatic stress disorder (PTSD), a condition that affects many survivors of overwhelmingly frightening events, such as war veterans or people who have been sexually assaulted. Not every trauma victim develops PTSD; women are twice as likely as men to suffer from it, although researchers do not know why.

Foa has been studying PTSD in rape victims and treating it since 1982; she co-authored a treatment manual published late last year. Even though PTSD has been recognized by the medical profession since 1980, public awareness is low, and many victims do not realize that they have a legitimate—and treatable—disorder. "A lot of them think the fact that they didn't overcome [the initial attack] means they're incompetent, something is wrong with them, or they're going to go crazy," she says.

Many people with PTSD suffer from anxiety and depression, and PTSD has been linked to physical illnesses, including heart disease, infections, and disorders of the digestive, respiratory and musculoskeletal systems. In addition, people with PTSD often lead tightly circumscribed lives, going to tortured lengths to avoid anything that might trigger unwanted memories or flashbacks. "Avoidance perpetuates the disability," explains Randall D. Marshall, director of trauma studies in the anxiety disorders clinic at the New York State Psychiatric Institute. "People start avoiding anything that can remind them of the trauma. Pretty soon you're in a deep hole, not dating, not having sex with your partner, not going to work or shopping or out by yourself. It can be severe and impairing."

According to figures from the Justice Department, in 1996 some 94,000 rapes and sexual assaults were reported in the U.S. But many more go unreported: the Justice Department estimates that the actual number of rapes and sexual assaults for that year was roughly 307,000.

Foa's research has shown that 95 percent of rape victims experience symptoms of PTSD during the first two weeks after being attacked. But after six months, the level has dropped to 35 percent, and it continues gradually to decline. If severe symptoms last a year, they are unlikely to resolve without treatment, Foa says. "It becomes chronic," she states. "Long term, anywhere between 13 and 20 percent of rape victims will develop chronic PTSD."

But, she declares, the vast majority can be helped with exposure therapy, which consists of nine 90-minute sessions with a therapist, along with a series of assignments to be completed between sessions. At the heart of the treatment lies a startling idea: that patients must confront the very memories they have been trying so hard to avoid.

"We ask them to close their eyes and relive the trauma and recount it aloud as if it's happening now," Foa explains. "The rationale is that if you allow yourself to actually recount the trauma and think about it, it will help you reframe it and understand in more realistic terms what actually happened. Because traumatic memories are encoded [in the brain] under extreme anxiety, they're encoded in not quite the same way as other memories. There are gaps. Time and space get confused. Recounting the story gives the client an opportunity to organize the narrative, and it's easier to deal with an organized narrative."

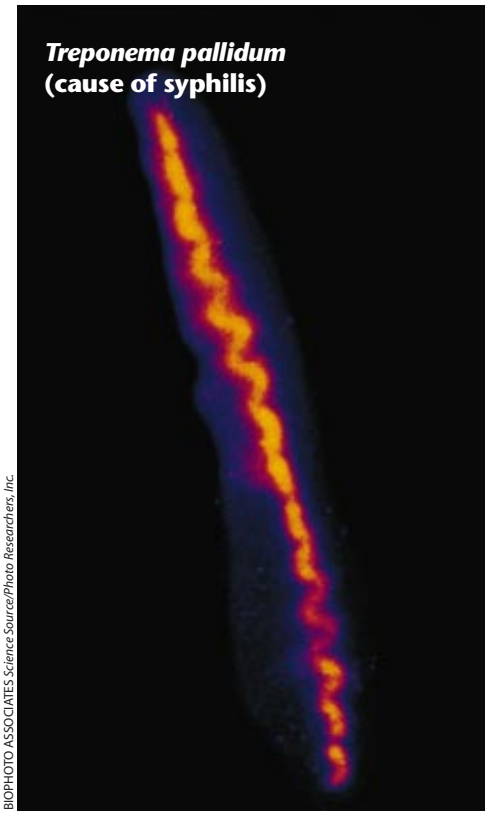
Patients tell the story again at each session and then listen to tapes of their accounts between sessions. If any aspects are especially upsetting, the therapist zeroes in on them and encourages the patient to go over them again. During the course of treatment a woman may repeat the account 20 to 30 times, sometimes more, Foa estimates.

At first, the narrative becomes longer, as the therapist encourages the patient to fill in details. Gradually, though, the account shortens as the patient drops many of the details and instead focuses on trying to make sense of what happened, Foa explains. Victims are often relieved to find that when they summon up the memory, nothing terrible happens to them.

"In our hands," Foa asserts, "90 percent of the clients show much improvement, and 75 percent lose the PTSD diagnosis completely. Also, most of them are not depressed anymore." Best of all, she remarks, exposure therapy is easy to teach to other therapists. Today Foa's technique is generally accepted as the standard method for treating rape victims. Marshall uses the technique, and he says that the program greatly accelerates the recovery process. In more difficult cases, he may prescribe antidepressant drugs.

Matthew J. Friedman, professor of psychiatry at Dartmouth College and executive director of the Department of Veterans Affairs's National Center for PTSD, uses exposure therapy to treat Vietnam veterans and is testing it in victims of childhood sexual abuse. "When you confront these intolerable, painful memories and feelings and develop ways of coping, they lose their capacity to terrify you and tyrannize your life," he declares.

Foa's patients report that exposure therapy helps them face aspects of their lives unrelated to having been attacked. "They learn you have to confront problems, not run away from them," Foa says. "This is teaching people about courage." SA



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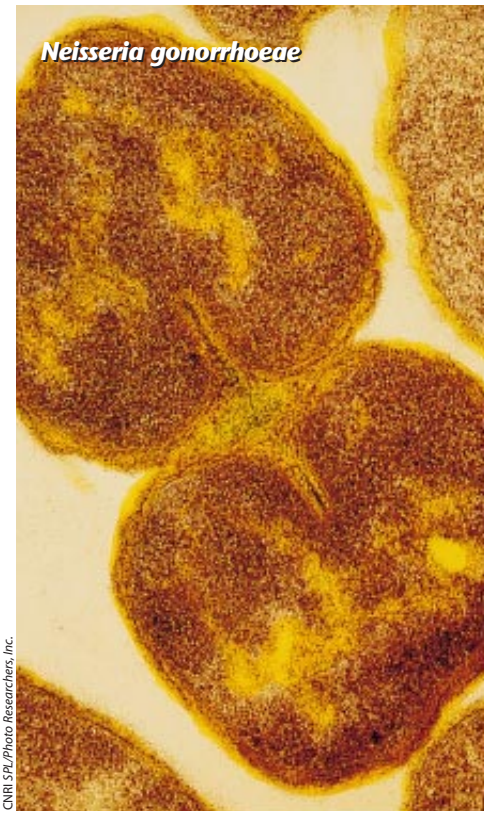

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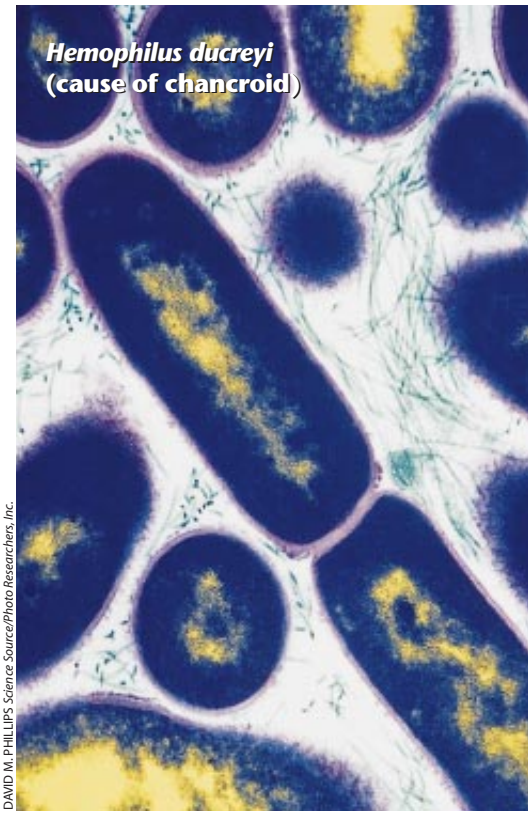

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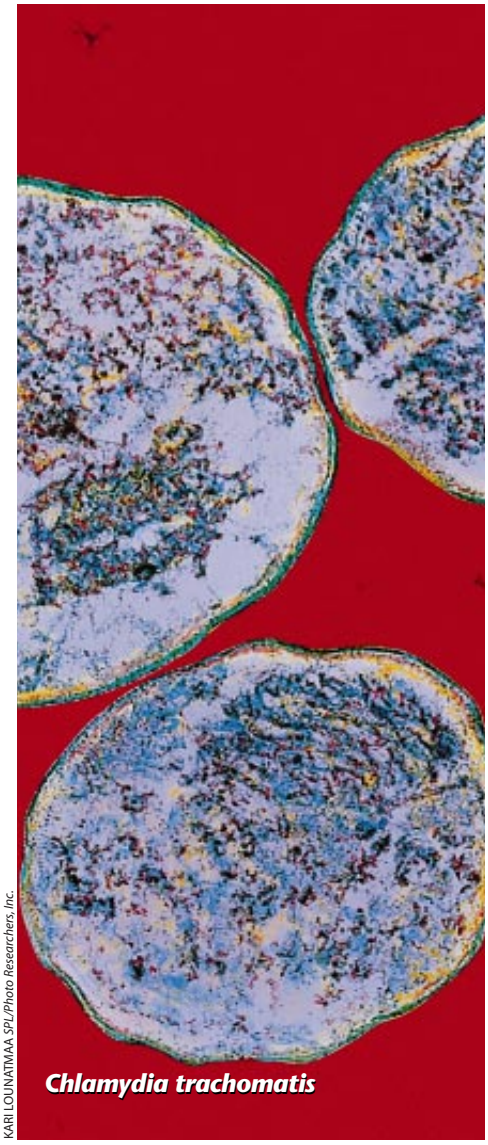

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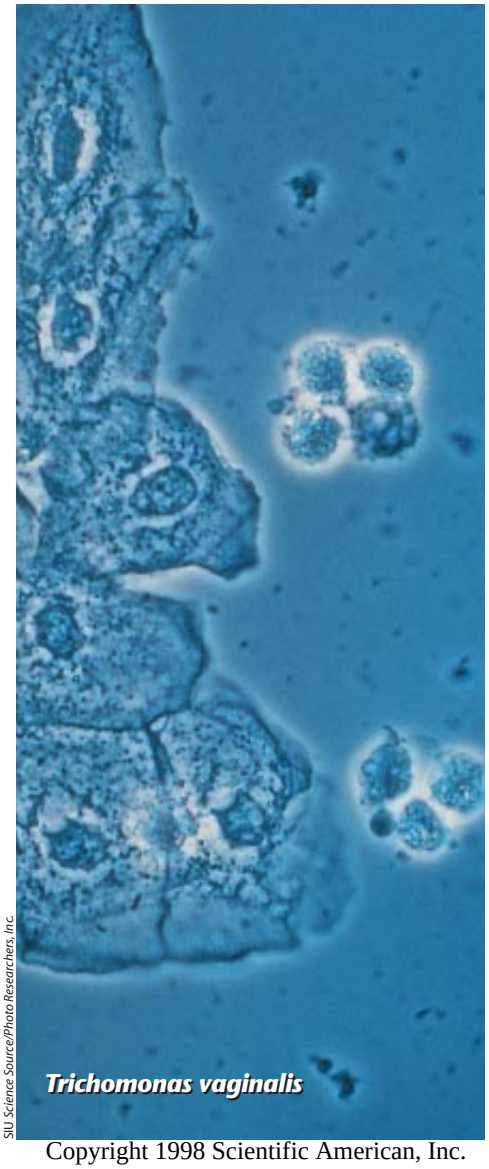

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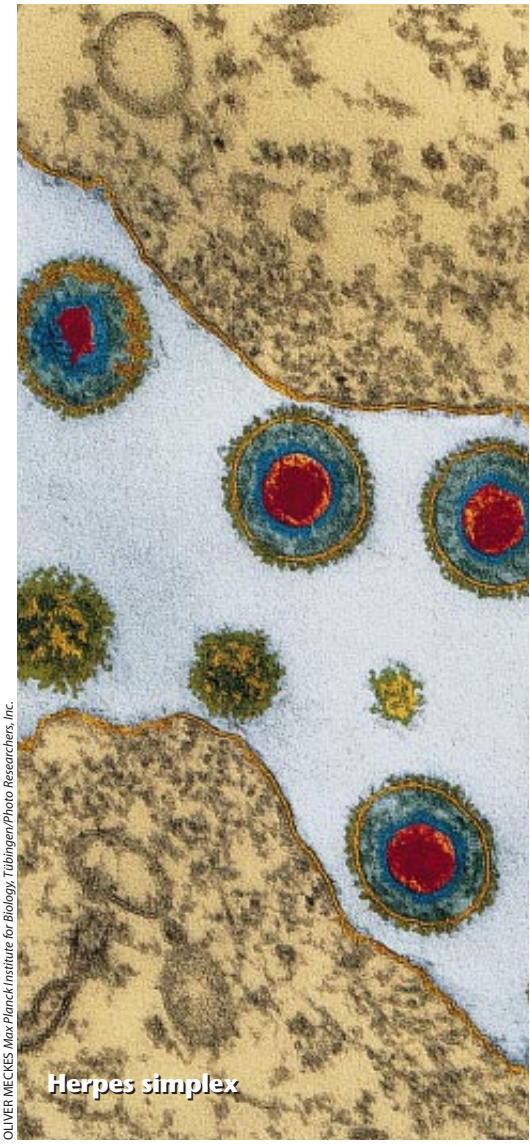


OLIVER MECKES *Max Planck Institute for Biology, Tübingen/Photo Researchers, Inc.*

What Women Need to Know about Sexually Transmitted Diseases

Left undiagnosed, STDs can be deadly. Fortunately, many people can be helped

by Laura A. Koutsky, Ph.D.
University of Washington

Half of all women will acquire one or more sexually transmitted infections during their reproductive years. Despite this dramatic statistic, most people think sexually transmitted diseases, or STDs, are rare. This misperception arises, in part, from the fact that people are often embarrassed to talk about sex, sexuality and gen-

italia. But frank discussion is needed. Every year 12 million or so new cases of STDs are reported in the U.S. The most common are chlamydia, gonorrhea and syphilis, which are caused by bacteria. The most widespread viral STDs are human papillomavirus (HPV), genital herpes, hepatitis B and human immunodeficiency virus, or HIV (the virus that causes AIDS). Among the consequences of these myriad STDs are ectopic pregnancy, infertility, preterm delivery, neurological disorders, arthritis, cardiovascular problems, cancer and even death.

This hidden epidemic primarily afflicts young people. Two thirds of STDs in the U.S. take place among people under the age of 25. This finding is not surprising: more than 60 percent of high school seniors report having had sexual intercourse, and 27 percent say they have had at least four partners. In 1971, 39 percent of young women between the ages of 15 and 19 reported having had more than one sex partner; in 1988 that figure reached 62 percent. There is no indication that this trend will reverse soon. Although our society does not condone adolescent sexual activity, the fact remains that teenagers are sexually active and that they are acquiring STDs with some painful consequences.

Rogue's gallery of microbes causes a variety of sexually transmitted diseases in millions of people every year.

This situation is especially disturbing because in many cases it is preventable. Although incidences of incurable viral STDs, such as HPV, appear to be similar everywhere, the incidence of curable bacterial STDs among U.S. teenagers and adults is higher than it is in other industrial countries. Syphilis, for example, afflicts 4.3 out of every 100,000 Americans annually—nearly three times the rate for Germans and almost 11 times the rate for Canadians. This discrepancy is caused in part by cultural differences in sexual behavior and by economic differences, but it also results from the fact that Americans have less access to diagnosis and treatment than do people in Germany or Canada—countries that provide universal health care. Indeed, one quarter of American adolescents and young adults do not have health insurance.

In developing countries, where health care resources are extremely limited, the situation is more dire. STDs, including syphilis, chlamydial infection, gonorrhea and pelvic inflammatory disease—an upper reproductive tract infection that can result from various STDs—constitute the second leading cause of healthy life lost for women between the ages of 15 and 44. Cervical cancer caused by genital HPV is the most common cancer and the principal cause of cancer-related deaths among women in these resource-poor countries,

where Pap tests are not widely available.

Although they affect both men and women, STDs are disproportionately damaging in women and adolescent girls. The biology of the female genital tract lends itself to asymptomatic infections. Unlike the male urethra, which often becomes painful within days of exposure to gonorrhea or chlamydia, the cervix (which is particularly susceptible to infection in younger women) may be infected for long periods without causing any discomfort. At least 25 percent of women with gonorrhea experience no symptoms, for instance, as opposed to less than 10 percent of men. Many women, unaware of the presence of an STD, do not seek medical attention—a delay that can have serious consequences. Untreated cervical gonorrhea and chlamydial infections can ascend into the uterus and fallopian tubes, causing pelvic inflammatory disease and setting the stage for ectopic pregnancies and infertility.

Some STDs are largely asymptomatic in both sexes—most men and women with HPV or herpes infections never become aware of them. Even so, women often suffer more damage to their health from these STDs: HPV infection, for instance, is more likely to cause cancer in women than in men [*see box below*].

Routes of Transmission

For many STDs, particularly the bacterial ones, people who repeatedly acquire and transmit infection play an important role in establishing and sustaining the prevalence of disease. Such people are considered to be high-frequency transmitters—in epidemiological terms, they are called a core group. This group typically includes people who are commercial sex workers, their clients and their partners, as well as men and women who have unprotected intercourse with multiple partners.

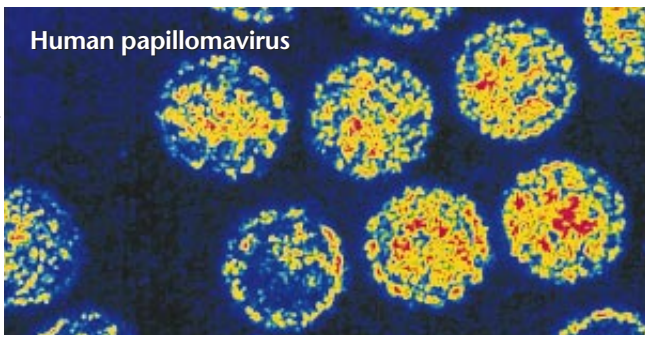
The impact of people in a core group appears to vary for different diseases. Syphilis requires the participation of a great many transmitters to achieve an annual incidence rate of 1 percent. HPV, however, can have an annual incidence rate of more than 5 percent in populations that include a tiny core group or even no core group at all. This difference may be explained by several factors. First, HPV appears to be more easily transmitted than *Treponema pallidum,* the bacterium that causes syphilis. Second, asymptomatic diseases are harder to control: more than 90 percent of genital HPV infections are asymptomatic; only about 50 percent of syphilis cases are. And, finally, current therapies usually do not rid the body of HPV infection, but penicillin can cure syphilis.

Whether STDs originate with a member of a core group or not, they are generally more efficiently passed during vaginal and anal intercourse than they are during oral intercourse. (In rare situations, an STD may be transmitted from a mother to her infant during pregnancy or delivery.) Furthermore, some STDs appear to be more easily transmitted from a man to a woman than from a woman to a man. For example, between 60 and 90 percent of women engaging in unprotected intercourse with men who have gonorrhea will become infected, whereas only 20 to 30 percent of men who have unprotected sex with infected women will contract the disease.

In the case of HIV, more data are needed to determine whether infection moves as readily from women to men as it does from men to women. It is clear, however, that HIV is somewhat more difficult to transmit during sexual intercourse than other STDs. The presence of syphilis, chlamydia, gonorrhea or chancroid may facilitate transmission of HIV. Rates of HIV infection are increasing faster among 15- to 44-year-old women than they are among any other group in the U.S.

The Challenge of Prevention

Women are at a distinct disadvantage with regard to protecting themselves against STDs. Synthetic condoms, which are the only available reliable barriers to infection, are generally in the control of the man. (The female condom does not seem to have become wildly popular; *see box on page 26*.) Nevertheless, sexually active women can reduce their chances of suffering the consequences of STDs. To do so, they should use a condom during intercourse with a new partner or with a regular partner who is unwilling to be monogamous. Sexually active women should undergo annual pelvic examinations and Pap tests, as well as screening for gonorrhea, chlamydia and HIV, if recommended by their health care provider.



ALFRED PASIEKA SPL/Photo Researchers, Inc.

The American Social Health Association (ASHA) is a nonprofit organization that provides information on HPV and other STDs. ASHA also sponsors the National STD Hotline (800-227-8922) and offers pamphlets and educational materials on STD-related topics. For more information, visit the organization's World Wide Web site at http://www.ashastd.org or write to the American Social Health Association/HPV, P. O. Box 13827, Research Triangle Park, NC 27709-3827.

Genital Human Papillomavirus

Human papillomavirus, or HPV, is a particularly insidious sexually transmitted disease (STD) because it is largely asymptomatic, can cause cancer and is virtually ubiquitous. More than 50 percent of sexually active adults have been infected with HPV—and less than 10 percent of them develop the warts that can help people identify an infection. As with other STDs, the incidence of HPV is highest among 18- to 28-year-olds. Most disturbing, perhaps, is the fact that condoms have not been shown to prevent transmission effectively, because HPV can occur in areas not covered by a condom—such as the base of the penis, the scrotum and the labia.

Of the more than 100 types of HPV, at least 35 infect the skin or mucosal surfaces of the genitalia (other types cause plantar warts and common skin warts). Although two types of HPV—HPV-6 and HPV-11—are most frequently detected in genital warts, these types are rarely found in invasive cancers of the cervix, vagina, vulva, penis and anus. Most such cancers seem instead to originate with infection by HPV-16, HPV-18, HPV-31 or HPV-45.

Genital HPV infections are primarily acquired through sexual intercourse. Unlike other viruses such as HIV and hepatitis B, HPV is not transmitted through blood and bodily fluids but rather by

ADRIENNE WEISS

Sexually Transmitted Disease	Percent of Women Who Show No Symptoms	Possible Long-Term Complications in Women	Effective Treatment or Vaccine Available?
Chlamydia	More than 75	Pelvic inflammatory disease, infertility, ectopic pregnancy, chronic pelvic pain	Antibiotics available; no vaccine
Gonorrhea	25–75	Pelvic inflammatory disease, infertility, ectopic pregnancy, chronic pelvic pain	Antibiotics available (although antibiotic-resistant strains exist); no vaccine
Syphilis	25–75	Cardiovascular problems, neurological disorders, damage to other organ systems	Antibiotics available; no vaccine
Chancroid	25–75	Unknown	Antibiotics available; no vaccine
Genital human papillomavirus	More than 90	Cervical, vulvar, vaginal and anal cancers	No*
Genital herpes	More than 50	Unknown	No*
Hepatitis B	25–75	Chronic liver disease, cirrhosis, liver cancer	No*; vaccine available
Human immunodeficiency virus	25–75	AIDS	No*
Trichomoniasis	25–75	Unknown	Antibiotics available

* Available treatments can reduce symptoms and complications but do not clear virus from the body. *SOURCE: Laura A. Koutsky and the Institute of Medicine*

Relying on over-the-counter products is no substitute for seeing a physician or nurse practitioner. Although douching is popular among some women, there appear to be few situations where it is medically required. Women with gonorrhea or chlamydia may actually increase their chances of developing pelvic inflammatory disease by douching. Women should also be aware that vaginal discharge does not always mean a yeast infection—rather it can be the sign of a more dangerous infection. Public health officials have recently become concerned that over-the-counter yeast infection treatments are encouraging women to diagnose and treat themselves, thereby delaying a trip to the doctor for a more serious problem, such as gonorrhea.

Despite this dismal state of affairs, there is hope. Researchers are working to develop vaccines for viral STDs, including HIV and HPV. A vaccine for hepatitis B is already available. And targeted behavioral intervention programs have proved successful in other countries. For instance, in Thailand, a government-sponsored and widely advertised effort to promote condoms among the general population and to enforce the universal use of condoms among sex workers has contributed to a dramatic decline in the incidence of STDs there.

There is growing awareness in the U.S. that the medical and public health community has not been effective in warning people about the rise in incidence of STDs or the possibilities for prevention and treatment. This ineffectiveness is clearly reflected in a 1993 survey, which found that 84 percent of women felt they were at no risk of contracting an STD. As many public health experts and a recent Institute of Medicine report note, the secrecy and uneasiness surrounding discussions of sex in the U.S. undermine this country's ability to address STDs. Without open discussion, education, outreach and intervention, the threats to young people will only continue with tragic consequences. SA

LAURA A. KOUTSKY, associate professor of epidemiology at the University of Washington, has studied the epidemiology of STDs for more than 10 years. Her research concerns genital human papillomavirus infection.

direct skin-to-skin contact. Although it is uncommon, warts on the fingers can carry genital HPV-6 or HPV-16, and in some cases, warts can develop in and around the mouth. All sexually active people—whether heterosexual or homosexual—are at risk of genital HPV infection with each new sex partner. Indeed, genital forms of the virus are not uncommon among lesbians.

Most newly acquired genital HPV infections do not announce themselves, and often people with genital HPV infection never become aware of its presence. HPV infection can be detected through certain tests for HPV DNA. Because of the high prevalence of this STD, any kind of general screening test for HPV would reveal infection in a huge proportion of sexually active adults. But the clinical importance of detecting asymptomatic infection in areas other than the cervix is not yet clear; penile cancer, for instance, is extremely rare.

The significance of genital HPV infection of the cervix, however, is quite certain. Precancerous lesions can form within a year of initial infection. Because early detection of cervical cancer is crucial for prevention and treatment, women should have regular Pap tests, which can detect HPV-related precancer, early invasive cancer and cancer of the cervix. Women should know that Pap readings are most accurate if they are done midway between menstrual periods. Gynecologists also recommend that women avoid vaginal creams, foams or suppositories the week before the exam and that they do not douche, have sex or use tampons the day before.

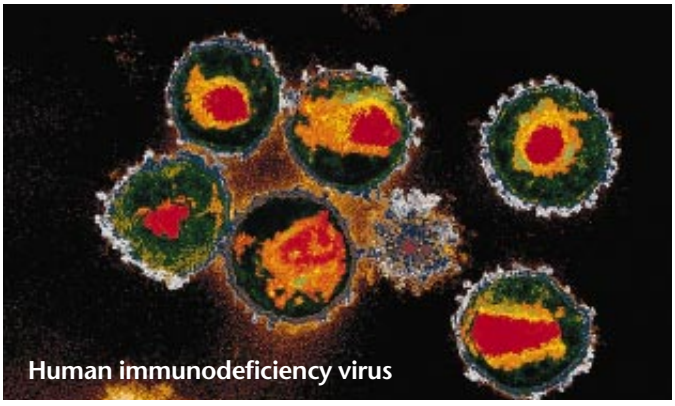
Women with abnormal Pap test results are referred for colposcopy. During this procedure, the cervix is treated with a mild vinegar solution and then examined for flat, whitish lesions. If these lesions prove to be precancerous or cancerous, they must be removed.

Genital warts in men and women can be surgically excised, frozen off or topically treated with medication, but the virus probably remains present in the body: it cannot be eradicated. For this reason, treatment of asymptomatic infection is not recommended.

In the near future, vaccines may be able to prevent HPV transmission. Our research group is testing an HPV vaccine that consists of the outer protein shell, or capsid, of the virus, which should stimulate the body's immune response, thereby preventing infection or disease. Similar vaccines have been effective in animals. If all goes well, an HPV vaccine may become available in the next decade. —*L.K.*

SCOTT CAMAZINE AND SUE TRAINOR/*Photo Researchers, Inc.*

The female condom's manufacturer, the Female Health Company, reports that the plastic vaginal sheath is 79 to 95 percent effective as a contraceptive and can reduce the risk of contracting HIV by 97 percent.



OLIVER MECKES E.O.S./Gelderblom/*Photo Researchers, Inc.*

Human immunodeficiency virus

Arm Yourself against STDs

Humanity's battle against sexually transmitted diseases (STDs) is limited by the weapons at our disposal. The bacteria and viruses that cause STDs are spreading faster than modern technology and education can sequester their populations. Although there are effective methods available for preventing infection, it is estimated that at least 300 million people are infected every year throughout the world with the most common STDs—gonorrhea, chlamydia, syphilis and trichomoniasis.

In addition to abstinence, there are three principal approaches to blocking the transmission of STDs: physical barriers, chemical barriers and vaccines. These techniques are in different stages of development and have various degrees of reliability.

Physical barriers

Physical barriers, such as synthetic condoms, prevent the organisms that cause disease from entering the body. Condoms are the only method of birth control on the market today that has proved effective in fighting most STDs. (They have not been shown, however, to block the transmission of human papillomavirus, or HPV.)

In addition to the male condom, there is a female condom available—sold under the brand name Reality. A package of three female condoms costs about $9, roughly the cost of 12 male condoms. But current studies by Family Health International are evaluating whether female condoms could be reused, notes Nancy Alexander, an expert on contraception at the National Institutes of Health. According to the manufacturer, The Female Health Com-

It's All Connected: The Importance of Addressing Young Men's Health

The waiting room is almost full, and it is only 4:30 P.M. Still half an hour to go before the clinic opens. The young men started arriving at 3:00, a few accompanied by their girlfriends, and they sit in rows facing a screen, watching a sexy music video. That is, until their viewing pleasure is interrupted by a slide show that opens with a graphic portrayal of the difference between an uncircumcised and a circumcised penis. The uncomfortable silence does not faze the social worker. "Any opinions on why they are different?" she asks. And the evening at the Young Men's Clinic at the Columbia University School of Public Health's Center for Population and Family Health in New York City is off and running.

For the next several hours, men and boys from the primarily Dominican, largely poor neighborhood of Washington Heights meet with doctors and nurse practitioners—as well as medical students from the New York and Presbyterian Hospital—to have HIV tests, physicals and exams for genital warts, herpes and other sexually transmitted diseases (STDs). "We use the slide show not to scare them but to open up discussion. We are trying to get them to challenge their beliefs," says Bruce Armstrong, associate professor of public health and co-founder of the clinic. About 80 percent of the young men who come in are sexually active, 40 percent have made a partner pregnant, and 17 percent have an STD; almost none of them receive health care anywhere else.

"It's teaching without preaching," adds Tschaka Tonge, one of the physician's assistants. "We talk to them about lifestyle. I ask the young gentlemen, 'Do you really need another girlfriend? Can you afford this?' We try to get them to rethink their choices."

In a small examining room, Tonge talks with a young man from Nigeria who says he needs a physical for college. Tonge knows some Yoruba and tries to get his patient to talk about his health and sexual activity: Has he been tested for tuberculosis? Where'd he lose his two front teeth? When did he become sexually active? Does he use birth control and, if so, which kind? Sabitu Ladejobi, who says he found out about the clinic from a flyer, is terse at first but slowly warms to his purple-shirted, dreadlock-sporting, hip-looking P.A.

The night of Ladejobi's visit is a particularly busy one. Not only is the free clinic—which is open only on Friday afternoons and Monday nights—filled to capacity as usual, but a group of Latin American public health experts are visiting. As one of a handful of places worldwide that offers preventive care for young men and that does not ignore their role in family planning, the Young Men's Clinic is increasingly being looked to as a model program.

Men have traditionally been left out of family-planning initiatives. Some of this bias has been purely practical: women have the babies, and most forms of birth control have been designed for them. Other aspects of the discrepancy have been incidental. "Put yourself in the mind-set of a young man who comes into a clinic and sees 50 women and a video on 'Your First Pelvic Exam' in the waiting room," Armstrong explains. "From the young fellow's point of view, the family-planning clinic is perceived as being for young women—even though that is not the policy."

New data on STDs and male sexual behavior, however, are beginning to inform family-planning strategies. In the late 1980s the first National Survey of Adolescent Males provided some of the only information on the attitudes and sexual behavior of 15- to 19-year-olds. The survey

pany, the female condom has proved effective in preventing the transmission of gonorrhea, chlamydia, syphilis and trichomoniasis—and if correctly used can reduce one's risk of getting HIV by as much as 97 percent. Alexander says that an independent study of the female condom's effectiveness in this regard has not yet been conclusive and is currently under way at the University of Alabama.

Because of its large size, the female condom has been somewhat unpopular since it went on the market in the U.S. in 1993, but the company says that sales are up and that the idea is catching on. The female condom consists of two rings connected by a polyurethane sheath. The small, inner ring covers the cervix, stretching the sheath to line the walls of the vagina. The larger ring at the other end of the sheath remains outside the woman, protecting the vaginal lips from contact with skin or bodily fluids.

Other barrier devices for women that rely on a combination of physical and chemical methods to block STDs are not as effective against infection, because they do not prevent fluids from entering the body. These methods include diaphragms and cervical caps.

Chemical barriers

Chemical barriers, such as spermicides, do not block the exchange of bodily fluids at all—but actively kill the viruses and bacteria that can cause disease on contact. Spermicides are not proved to be effective in preventing most STDs, however—not because they cannot kill the organisms but because they cannot kill all of them.

To be effective, a chemical barrier must be applied to cover every place that bodily fluids might travel during sex, a task that is nearly impossible. Yet there is some evidence suggesting that spermicides are an effective defense against chlamydia and gonorrhea, Alexander says. And although some researchers are developing spermicides that will be able to target specific viruses or bacteria, any chemical barrier will still be limited by its inability to protect all sexually exposed areas.

Vaccines

Perhaps the greatest hope for defense against STDs lies in vaccines, which activate the body's immune system to attack the organisms that can cause disease. The only STD vaccine available is for the viral infection hepatitis B. The Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend the vaccine for all newborns, children and sexually active people.

Several vaccines are being tested to fight HIV, but so far none has been effective. The search for a vaccine is hampered by the fact that investigators do not yet understand how—or even whether—the human body can resist the ravages of HIV.

The quest for a vaccine for HPV—the virus associated with 90 percent of cases of cervical cancer—has just begun. Still, researchers are hopeful because animal vaccines against analogous infections, such as bovine papillomavirus in cows, have been effective.

Despite the promise of STD vaccines, Alexander predicts that they will not be available for another 20 years. The process is slow because vaccines have to be tested on humans—and precautions must be taken to prevent the spread of disease while testing the effectiveness of the treatment.—*Krista McKinsey, special correspondent*

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recently found that between 1988 and 1995 the use of contraceptives during first intercourse increased from 62 to 73 percent; condom usage, in particular, rose significantly.

The survey's authors also found that, contrary to stereotype, 90 percent of men believe they should talk to their partner about contraception before intercourse, protect against pregnancy and take responsibility if they do father a child. These findings, as well as a review of male-oriented programs, were recently published in an Urban Institute report, "Involving Males in Preventing Teen Pregnancy."

Public health experts say the shift to include men is part of a larger social transformation catalyzed by the current fatherhood movement, the 1988 Family Support Act—which requires noncustodial parents to be financially responsible for their progeny—and the 1995 Clinton administration effort to design federal programs that include and promote the involvement of fathers. Developing "the role of men as being nurturing, caring and responsible in reproductive health matters has taken a while in many ways," Armstrong remarks. "It was just a short time ago that fathers were not allowed into the delivery room."

But perhaps most responsible for the changing approach is the alarming prevalence of STDs. According to the Alan Guttmacher Institute, 12 million such infections occur annually in the U.S.—among the highest numbers in the industrial world—and teenagers account for 25 percent of all cases. Judith N. Wasserheit, director of the Division of STD/HIV Prevention at the Centers for Disease Control and Prevention, notes that men have been the focus of STD programs in the past, largely because most STDs are more symptomatic in men. But in the past decade or so, more data have made clear the long-term consequences of asymptomatic STD infection in women—including infertility, cervical cancer, miscarriage, stillbirth, premature delivery, and mental retardation and blindness in newborns. Now, Wasserheit says, "there is a very interesting confluence with the family-planning community's saying we need to do more for men, and the STD community's saying we need to do more for women."

"Although you are talking about women's health, men are very much interwoven," concurs Anidolee Chester, education coordinator at Planned Parenthood in Providence, R.I. "If you get them to have some sense of responsibility, you will see improvements in women's health." Chester and her colleagues recently started a program for men, modeled after the Young Men's Clinic.

Armstrong and his colleagues say the clinic's success comes from their efforts to make every moment a "teachable" one and to listen without judging. "There is a stereotype that young men are healthy, not concerned about health, and hard to engage and maintain as patients," says Alwyn T. Cohall, medical director at the clinic and director of the Harlem Center for Health Promotion and Disease Prevention. "We have debunked all of these myths." —*Marguerite Holloway, contributing editor*

MARTIN SCHOELLER *SABA*

Discussions at the Young Men's Clinic in New York City emphasize men's roles in family planning.

Single-Sex Classrooms: Are They Best for Girls?

Girls-only classes are gaining in popularity, but whether they help girls to learn is still an open question

by Karyn Hede, *special correspondent*

The popular musical group the Spice Girls calls it "Girl Power." It's that intangible feeling of self-worth that some girls have—and others don't. But ask a group of researchers and educators how best to boost a girl's self-esteem, which is thought to be key to academic success, and the arguments begin.

The idea that all-female secondary schools do a better job of instilling a sense of academic competence and accomplishment is spreading across the U.S. Enrollment in the 84 public and private girls' schools that are members of the National Coalition of Girls' Schools (NCGS) has increased 15 percent since 1991. And in the past three years, 18 new all-girl schools—seven of them public—have opened their doors in the U.S.

But a report issued in March by the American Association of University Women (AAUW) challenges the notion that "girls only" is the best approach to educating young women. After an exhaustive review of available research on single-sex classrooms in public, private and parochial schools worldwide, a panel of educators and researchers concluded that there is no evidence in general that a same-sex environment helps girls do better in school.

Then why are so many school boards taking a gamble on all-girl schools? Many trace the trend to a set of research articles that shook up educators in the mid-1980s. Among the most often cited is a three-year study of more than 100 fourth-, sixth- and eighth-grade classrooms by David and Myra Sadker of American University. The Sadkers found that both male and female teachers tend to favor boys and to downplay girls' contributions and to discourage girls unintentionally from achieving in traditionally male-dominated subjects such as math and science. According to the researchers, boys receive more frequent and precise feedback, such as clear criticism and praise from teachers, whereas girls receive less classroom attention, leading to decreased standardized test scores and self-esteem.

Child psychologist Mary B. Pipher added to the negative perception of coeducation with her 1994 best-seller *Reviving Ophelia: Saving the Selves of Adolescent Girls*. In the book, Pipher describes how girls are demeaned by the pattern of sexual harassment by adolescent boys they often face at school.

To remedy such ills, the state of California last year opened six pairs of experimental single-gender "academies" within existing public schools across the state, each funded by a $500,000 grant from a state appropriation. New York City opened a public all-girl school in 1996, and similar experiments are being considered in cities from Seattle to Presque Isle, Me.

Girls, Math and Science

Barbie said, "Math is hard," and parents and teachers across the country scurried to prevent girls from getting the message that it's feminine not to like math.

But while educators strive to ensure that girls are given every opportunity to achieve in traditionally male-dominated fields such as math and computer science, some scholars are asserting that teachers and administrators must first recognize that girls relate to these subjects differently than boys.

The stakes are high: women who stick with math and science earn more than their counterparts who don't. And the well-recognized gender gap in wages virtually disappears for women in their 30s who have earned eight or more credits of college-level mathematics, as reflected in 1991 Department of Education statistics. Yet girls still tend to avoid these subjects, and because of it they continue to be underrepresented in high-paying math, computer science and engineering jobs.

Many feminist scholars say girls will succeed in math and science more often if teachers present the material in a "girl-friendly" way. Psychologist Carol F. Gilligan argues that girls learn best by making connections, whereas boys are more comfortable with abstract concepts and working things out individually—the way subjects like math and science have usually been taught.

"Girls have different ways of knowing," says Suzanne K. Damarin of Ohio State University. She asserts that girls learn abstract concepts best if they are placed in the context of personal experience. Traditionally, Damarin observes, math concepts are presented in a language of hierarchies, power and competition that girls learn to avoid.

Damarin believes that single-sex schools are a good idea when they are implemented thoughtfully, because such environments allow girls to explore fields such as computer science that can be too intimidating in a coed situation. In some coed classes, teachers introduce students to computers using competitive games in which the on-screen "heroes" are male and students compete against one another or the computer for points. Most girls prefer a cooperative environment, according to Dam-

ARMEN KACHATURIAN *Gamma Liaison Network*

Girls participate in a science class at New York City's Young Women's Leadership School.

Proponents of all-girl schools point to studies showing that girls emerge from a single-gender educational environment more confident in their abilities and more likely to feel comfortable in math and science classes than girls from coeducational schools. "I think it's the culture of an all-girl environment that really puts a solid flooring under girls as they get involved in their schoolwork," says Whitney Ransome, executive director of NCGS. "There is no subtle message that they can't do something. It's a real can-do culture."

But the new report, entitled "Separated by Sex," reveals that although girls report higher self-esteem in single-sex classes, for most this does not translate into higher test scores or a propensity for a career in math and science. The one exception appears among minority girls, who seem to thrive in single-gender classrooms as compared with peers who are educated in coed classes. Researchers ascribe these differences to an atmosphere that empowers minority students to excel.

Other recent studies suggest that single-sex classes and schools not only do not lead to higher grades but in fact can actually reinforce traditional gender stereotypes that can hinder girls' achievements. For example, in a 1994 study of 21 schools across the U.S., University of Michigan researchers Helen M. Marks (now at Ohio State University) and Valerie E. Lee found that gender stereotyping—reinforcing the cultural norms of masculine and feminine behaviors—occurs as often in single-sex schools as in coed schools.

Lee, who is a co-author of the AAUW report, has conducted studies showing that Catholic all-girl schools improve the students' academic performance. Still, subsequent efforts to duplicate her research in nonparochial all-girl schools have caused her to have second thoughts about single-sex schooling.

Lee adds that instituting single-sex classes within coed schools can backfire. "People never think about what the ripple effects are going to be throughout the rest of a coeducational institution if you start offering physics or math classes just for girls," she says. "Not all girls are going to want that option. So you end up siphoning off some girls and having even fewer girls in the coeducational class."

Such criticisms might fuel already pending complaints such as the one against New York City's recently opened Young Women's Leadership School brought under Title IX of the Education Amendments of 1972 by the New York Civil Liberties Union and by the New York chapter of the National Organization for Women. Title IX prohibits school districts from discriminating against students on the basis of sex.

So what works for girls? The AAUW report concludes that small class size, a rigorous academic curriculum and teachers who are involved in helping all students achieve are more important than whether a boy sits at the next desk.

Janice Weinman, executive director of AAUW, says she hopes the report will slow some of the rush to institute all-girl education in public schools. "We'd like people to take a second look at whether there should be support and funding for single-sex classrooms in a public school setting," she says.

Yet the demand for all-girl schools remains strong. "What we need in this country is a variety of educational options," Ransome asserts. "We know more research is needed. But we also know from our own observations and decades of experience with all-girl settings that it does make a difference." SA

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arin, where teams work together and there is no fixed "right way" to solve a problem.

But other educators caution that overgeneralizing girls' innate interests and abilities can make girls who are already interested in math and science feel like something is wrong with them. Researchers such as Patricia B. Campbell, president of Campbell-Kibler Associates, an educational consulting firm in Groton, Mass., says that discussing sex differences between boys and girls only reinforces gender stereotypes. "If you are 13 and you have interests in math and numbers and people are telling you math's not for girls, that's devastating," she says.

Campbell challenges the notion that girls have different learning styles. The differences between individual girls and boys are much greater than between the "average" girl or boy, she notes. The key to having girls succeed in math and science is identifying strategies to teach those subjects that work for both girls and boys, she states.

Despite the continuing disparity between the achievements of girls and boys in math and science, things might be beginning to change. "Girls continue to underaspire," says Janice Weinman, executive director of the American Association of University Women (AAUW). "But we have made progress, particularly in the area of test scores, where the gap appears to be closing."

The test scores of U.S. 12th graders had one of the smallest gender gaps of the 41 nations that participated in the Third International Mathematics and Science Study, which was released in February—although U.S. students scored well below the international average. But data from the 1996 National Assessment of Educational Progress showed that even though fourth- and eighth-grade boys and girls had similar test scores in science, by the 12th grade, boys scored higher than girls.

So what does it take to keep girls engaged in math and science? There are hundreds of new programs that try to get girls involved in these subjects, but few have more than anecdotal evidence that they are doing any good. The problem, Campbell offers, is that most programs aren't doing follow-up research on how well they achieve their goals. "One program for girls I evaluated actually showed that doing nothing was better than doing something," she says.

The Department of Education has established expert panels to review the educational programs in individual schools that have managed to keep both girls and boys interested in math and science. The panel is charged with recommending which of the schools has programs that others should adopt. The first panel, which is evaluating math programs, is expected by mid-1998 to designate programs that work, according to program coordinator Susan Klein. "The goal is to highlight programs that demonstrate excellence and make the information available nationally," she says.

But educators already agree that the best math and science programs for girls have several things in common. In a 1995 report entitled "Growing Smart: What's Working for Girls in School," the AAUW concluded that successful programs place girls in cooperative learning groups that eliminate a competitive environment; provide girls with mentors and role models; give girls plenty of access to computers and lab equipment; and work with community groups to help girls achieve goals. —*K.H.*

NAJLAH FEANNY *SABA*

Why Are So Many Women Depressed?

Women may be more sensitive—physiologically, at least—to certain changes in the environment. And this responsiveness might help explain the high rates of depression in their ranks

by Ellen Leibenluft, M.D.
National Institute of Mental Health

The symptoms of depression range from uncomfortable to debilitating: sleep disturbances, hopelessness, feelings of worthlessness, difficulty concentrating, fatigue and sometimes even delusions. Most of us have watched a relative or friend struggle with depression—and many of us have experienced it ourselves. Even so, few people realize just how common depression is, how severe it can be or that it is most prevalent among women. In 1990 the World Health Organization found depression to be the leading cause of "disease burden" (a composite measure including both illness and death) among women, noting that it affects almost 20 percent of the female population in the developed world. Epidemiological studies indicate that 12 percent of U.S. women—compared with only 6 percent of U.S. men—have suffered from clinically significant depression at some time in their lives.

The big question, of course, is why such a gender gap exists. Over the years various explanations have surfaced to account for the fact that, from one study to the next, depression is between two and three times more common among women than it is among men. Some mental health workers have pointed to psychology, arguing that women are better trained to recognize their feelings and seek help, so they come to the attention of health professionals more often than men. Others have suggested that oppression—in the form of physical or sexual abuse, harassment or discrimination—is to blame. Others still have attributed the increased rates of depression among women to the female reproductive system and the menstrual cycle.

Medications known as selective serotonin reuptake inhibitors (SSRIs), which are often most effective when used in conjunction with psychotherapy, were approved for treating depression in the late 1980s. These drugs, which include Prozac, Paxil and Zoloft, act on the brain by regulating the neurotransmitter serotonin.

But it isn't that simple. Data from a variety of studies show that depression clearly has psychological, environmental and biological roots. Modern neuroscience is beginning to teach us how these roots can become intertwined and reinforce one another. In other words, an increased risk for depression in women might stem from genetics, the effects of stressful events or social pressures, or some combination of all three. Neuroimaging of the brain's circuitry by PET and MRI scans reveals that psychological phenomena such as anger and sadness have biological underpinnings; we can now see circuits of brain cells becoming activated when these emotions arise.

Similarly, neuroimages demonstrate that environmental and psychological experiences can alter our brain chemistry. For example, Lewis R. Baxter and his colleagues at the University of California at Los Angeles found similar changes on the PET scans of patients with obsessive-compulsive disorder who responded to treatment, regardless of whether the patients were treated with medication or with behavioral therapy.

To figure out why depression is more common among women, scientists have to study how genetics and environment divide the sexes—and how the two conspire to produce the symptoms we describe as depression. It is difficult work, and progress is necessarily slow. But what is coming into focus is that certain environmental factors—including stress, seasonal changes and social rank—may produce different physiological responses in females than they do in males. These findings, which I will outline, are small pieces in what is proving to be an incredibly complex puz-

Psychotherapy has long proved valuable in alleviating symptoms of depression. More than 80 percent of all depressed patients now respond to therapy or medication, or a combination of the two.

zle. Laying them out at this stage does not begin to explain depression's double standard. Nevertheless, it could help scientists develop more effective treatments for depressed individuals—both women and men—in the meantime.

Stress and Cortisol

Many scientists have wondered whether there is some quirk in the way depression is inherited, such that a depressed parent or grandparent is more likely to pass on a predisposition for the disorder to female than to male descendants. Based on studies that trace family histories of depression, the answer to that question appears to be no. Women and men with similar heritage seem equally likely to develop the disorder. Simply tracing family histories, though, without also considering environmental influences, might not offer a complete picture of how depression is inherited.

Indeed, Kenneth S. Kendler and his colleagues at the Medical College of Virginia found in a study of 2,060 female twins that genetics might contribute to how women respond to environmental pressures. The researchers examined twins with and without a family history of depression; some twins in both groups had recently undergone a trauma, such as the death of a loved one or a divorce. The investigators found that among the women who did not have a family history of depression, stressful events raised their risk for depression by only 6 percent. But the same risk rose almost 14 percent among the women who did have a family history of depression. In other words, these women had seemingly inherited the propensity to become depressed in the wake of crises.

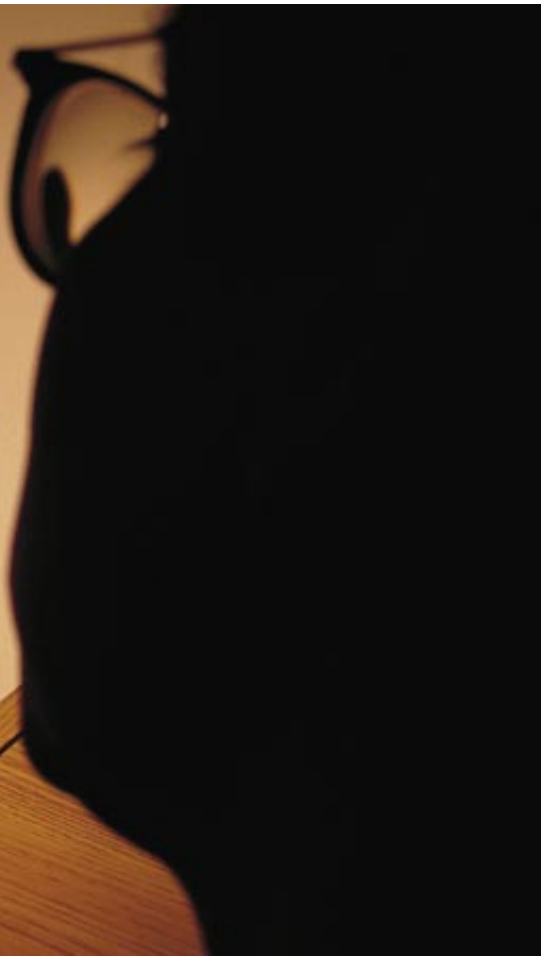
A similar study has not been done in men, leaving open the question of whether environmental stress and genetic risk for depression interact similarly in both sexes. But research is being done to determine whether men and women generally experience similar amounts and types of stress. Studies of key hormones hint that they do not. Hormones are not new to depression researchers. Many have wondered whether the gonadal steroids estrogen and progesterone—whose cyclic fluctuations in women regulate menstruation—might put women at a greater risk for depression. There are at least two ways in which they might do so.

First, because of differences between the X and Y chromosomes, male and female brains are exposed to different hormonal milieus in utero. These hormonal differences may affect brain development so that men and women have different vulnerabilities—and different physiological reactions to environmental stressors—later in life. Indeed, animal experiments show that early hormonal influences have marked behavioral consequences later on, although the phenomenon is of course difficult to study in humans.

Second, the fact that postpubertal men and women have different levels of circulating gonadal steroids might somehow put women at higher risk for depression. Research shows girls become more susceptible to depression than boys only after puberty, when they begin menstruating and experience hormonal fluxes. Even so, scientists have never been able to establish a direct relation between emotional states and levels of estrogen and progesterone in the blood of women. For example, Peter J. Schmidt and David R. Rubinow of the National Institute of Mental Health recently reported that manipulations of estrogen and progesterone did not affect mood, except in women who suffer from severe premenstrual mood changes.

It now appears, however, that estrogen might set the stage for depression indirectly by priming the body's stress response. During stressful times, the adrenal glands—which sit on top of the kidneys and are controlled by the pituitary gland in the brain—secrete higher levels of a hormone called cortisol, which increases the activity of the body's metabolic and immune systems, among others. In the normal course of events, stress increases cortisol secretion, but these elevated levels have a negative feedback effect on the pituitary, so that cortisol levels gradually return to normal.

Evidence is emerging that estrogen might not only increase cortisol secretion but also decrease cortisol's ability to shut down its own secretion. The result might be a stress response that is not only more pronounced but also



NAJLAH FEANNY *SABA*

longer-lasting in women than in men.

For example, Nicholas C. Vamvakopoulos, George P. Chrousos and their colleagues at the National Institute of Child Health and Human Development recently found that increased levels of estrogen heighten the activity of the gene for human corticotropin-releasing hormone (CRH). This gene controls the secretion of CRH by a region of the brain called the hypothalamus. CRH makes the pituitary gland release adrenocorticotropic hormone (ACTH), which circulates in the blood and eventually reaches the adrenal glands, where it prompts the secretion of cortisol. Thus, estrogen can, by increasing CRH secretion, ultimately boost cortisol secretion. And Elizabeth A. Young of the University of Michigan and others have shown that female rats are more "resistant" to cortisol's negative feedback effects than are either male rats or spayed female rats. She has also shown that women have longer-lasting cortisol responses during the phase of the menstrual cycle when estrogen and progesterone levels are high.

It is unclear whether depression is a cause or a consequence of elevated cortisol levels, but the two are undoubtedly related. Over the past few decades, a number of studies have shown that cortisol levels are elevated in about half of all severely depressed people, both men and women. So the idea is this: if estrogen raises cortisol levels after stress or decreases cortisol's ability to shut down its own secretion, then estrogen might render women more prone to depression—particularly after a stressful event.

Light and Melatonin

Despite their importance, estrogen and cortisol are not the only hormones involved in female depression, and stress is not the only environmental influence that might hold more sway over women than men. Recent findings by Thomas A. Wehr, Norman E. Rosenthal and their colleagues at the National Institute of Mental Health indicate that women might be more responsive physiologically than men to changes in exposure to light and dark. These investigators have had a long-standing interest in seasonal affective disorder (SAD), or so-called winter depression (although it can occur in the summer as well), and the role that the hormone melatonin might play in the illness. Similar to the gender ratio in other forms of depression, SAD is three times more common in women than in men.

Melatonin has been a prime suspect in SAD because organisms (including humans) secrete it only when they are in the dark and only when the body's internal clock (located in the hypothalamus) believes it is nighttime. The pineal gland, a small structure that resides deep in the mammalian brain, begins to secrete melatonin in the evening, as daylight wanes. Melatonin levels drop in the morning, when light hits the retinas of the eyes. Because nights are longer in winter than in summer, animals living in the wild secrete melatonin for longer periods each day during winter. Among animals that breed in summer, the onset of this extended daily melatonin secretion signals the presence of winter and shuts down the secretion of gonadal steroids that facilitate reproduction.

SAD researchers have long wondered whether a wintertime increase in the duration of melatonin secretion might also trigger depressive symptoms in susceptible individuals. In a series of ongoing studies designed to address this question, Wehr and his colleagues first asked whether humans, like animals, undergo seasonal changes in melatonin secretion. It is an important question, given that artificial light provides humans with an "endless summer" of sorts compared with animals in the wild. To find out, Wehr measured melatonin secretion in 15 humans when they were exposed to 14 hours of darkness and later to only eight hours of darkness each night. The results of this experiment, conducted mostly among men, were positive: people experiencing longer periods of darkness secreted melatonin for longer periods during the night, as wild animals do.

Next, the researchers asked whether this natural sensitivity to the seasonal day-length change persisted when people were allowed to follow their usual schedules, turning on artificial lights at night as they normally would. Here the researchers were surprised to find a gender difference. Under normal living conditions, women were more likely than men to retain a sensitivity to seasonal changes in day length. In other words, for women the duration of nocturnal melatonin secretion was longer in winter than summer; in men, however, there was no seasonal difference.

These results suggest that women are more sensitive to natural light than men—and that in a society where artificial light is everywhere, women somehow still detect seasonal changes in natural day length. Whether this gender difference puts women at increased risk for SAD is unclear; paradoxically, there is evidence that women with SAD symptoms may be less likely than unaffected women to have an increased duration of melatonin secretion in winter.

To complicate the story further, the relation between these findings and those regarding cortisol and estrogen are also unclear, because we don't know whether the duration of melatonin secretion affects reproductive function in women, as it surely does in animals. Researchers are now working to unravel the complicated relations between these hormonal systems and to determine whether, and how, they may influence individuals' risk for depression.

Social Rank and Serotonin

If women's bodies are in fact particularly sensitive to environmental changes, the explanation may lie within the system that controls serotonin, one of many so-called neurotransmitters that nerve cells use to communicate with one another. Serotonin modulates both cortisol and melatonin secretion. (The similarity in

PHOTOGRAPHS BY NAJLAH FEANNY *SABA*

Treatment alternatives such as light therapy (top) *and electroconvulsive therapy (ECT)* (bottom) *are used in special cases. Light therapy seems particularly effective in patients with the form of depression called seasonal affective disorder (SAD). ECT is most often used as a last resort, when all other treatment options have failed.*

names between serotonin and melatonin is no accident: the latter is synthesized directly from the former, and the two have very similar chemical structures.) And a great deal of evidence indicates that dysfunction in the serotonergic, or serotonin-secreting, system contributes to depression and anxiety disorders, which are also more common in women than men. Recently research in animals and humans has provided preliminary, but key, insights into this system.

First, it appears that the serotonergic system serves as a link between an animal's nervous system and its physical and social environment. That is, not only do stress and daylight act via the serotonergic system but an animal's social rank also appears to affect its serotonin level. A number of studies show that blood and brain serotonin levels change as an animal moves up or down dominance hierarchies. For instance, dominant male monkeys often have higher blood serotonin levels than subordinate ones do. In addition, a recent study by Shih-Rung Yeh and his colleagues at Georgia State University shows that the sensitivity of an animal's neurons to serotonin varies according to that animal's status. Specifically, Yeh found that neurons taken from crayfish that had recently won a fight responded to serotonergic stimulation more strongly than neurons taken from losing crayfish.

There also appear to be significant gender differences in the serotonergic systems of both animals and humans. Mirko Diksic, Sadahiko Nishizawa and their colleagues at McGill University recently provided the most dramatic example: to measure serotonin synthesis in the human brain, they devised a new technique using PET neuroimaging and found that the average synthesis rate was 52 percent higher in men than in women. The investigators note that with the exception of estrogen binding sites, this gender difference in the brain is one of the largest ever reported. The lower rate of serotonin synthesis in women might increase their overall risk for depression—especially if serotonin stores are depleted during stress or winter darkness.

A Gender Difference

Meir Steiner and his co-workers at McMaster University suggest that if serotonin mediates between an organism and its environment and if the neurotransmitter is regulated differently in men and women, it might explain gender patterns not only in depression but also in a range of psychiatric illnesses. Specifically, whereas depression and anxiety are more common among women, alcoholism and severe aggression are more common among men. And just as low serotonin levels have been implicated in depression and anxiety disorders in women, they have also been found in the brains of men with severe forms of alcoholism and aggression.

Such gender differences in the serotonergic system might ensure that females respond to stress with psychiatric disturbances that involve behavioral inhibition, whereas men respond to stress with a loss of behavioral control. Steiner suggests that such gender differences in the serotonergic system evolved because child rearing is more successful (in the narrow sense of more children surviving to adulthood) in species in which aggressive impulses are curtailed in females.

A researcher espousing either the sociological or psychological explanation of depression's gender bias might counter Steiner's theory by arguing that men are socialized to respond to stress with "act-

ing out" behaviors, such as alcoholism or aggression. In contrast, society teaches women to respond to stress with "acting in" behaviors, such as depression. To support this idea, they might point to epidemiological studies done in Amish and Jewish populations. In these communities, alcoholism is less common than in the population at large, and, interestingly, the rates of depression are as high in men as in women.

These contradictory data leave no doubt that the explanations behind depression and other psychiatric diseases are not straightforward. Biological and social influences not only coexist but also probably reinforce one another. After all, we would expect gender socialization patterns to evolve so that they complement biological differences between the sexes. In other words, we would expect "nurture" to reinforce rather than oppose "nature." And because nurture involves learning—and learning occurs when certain neural connections in the brain are strengthened—it is clear that both nurture and nature involve biological processes.

Scientists have made tremendous strides in treating depression. With the advent of such antidepressants as Prozac (which acts on the serotonergic system), more than 80 percent of depressed patients now respond to medication or psychotherapy, or a combination of the two. But much more work remains to be done. Because depression is so common, its cost to society is high. The National Institute of Mental Health estimates that depression claims $30.4 billion in treatment and in lost productivity from the U.S. economy every year.

And these costs are on the rise: depression is becoming more common in successive generations (the so-called cohort effect). No one knows what is causing the cohort effect—but it is moving much too quickly to have a genetic basis. Theories about what is causing the cohort effect range from increased drug abuse and familial disarray to the suggestion that perhaps older people are simply more likely to forget past depressive episodes when asked. The cohort effect and depression in general remain very much a mystery. And for the men and women who suffer from it, it is a mystery that cannot be solved soon enough. SA

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Treating PMS with Antidepressants

From time to time, almost all women experience what is known as premenstrual syndrome (PMS): mild cramping, bloating, irritability and fatigue. For some, the symptoms preceding menstrual periods are debilitating. An estimated 3 to 5 percent of all women suffer from marked distress, anger, tension and mood swings every month. For these women a range of remedies—including progesterone, estrogen, diuretics, vitamins, herbs and mineral preparations—have proved useless.

The bad news is that no one has figured out exactly what causes the condition—which psychiatrists now call premenstrual dysmorphic disorder (PDD). But scientists have found that a class of antidepressants, called selective serotonin reuptake inhibitors (SSRIs), can alleviate PDD in some patients. These medications represent a big improvement over the only previous solution—surgically removing the ovaries. And the fact that these drugs help also underscores the point that PDD has a biochemical basis. It is not—as many women have been told by their physicians—something they imagine.

Most evidence suggests that women with PDD have deficiencies in the neurotransmitter serotonin. SSRIs, such as Prozac, Zoloft and Paxil, act in the brain to raise serotonin levels. Studies show that tryptophan, an amino acid the body uses to make serotonin, can relieve symptoms of PDD, and laboratory tests reveal that women with PDD have abnormal blood levels of serotonin. In addition, the disorder often causes women to crave carbohydrates, a symptom that is also associated with a dearth of serotonin.

Since SSRIs were introduced in the late 1980s, roughly a dozen studies have demonstrated their efficacy in treating PDD; last year a large investigation—involving more than 200 women and 12 medical centers—corroborated the finding. Kimberly Yonkers of the University of Texas Southwestern Medical Center at Dallas and her colleagues published in the *Journal of the American Medical Association* that 62 percent of women treated with the SSRI sertraline (Zoloft) improved, compared with only 34 percent of women who received a placebo. It is unclear whether SSRIs can alleviate less severe forms of PMS, but further research should lead to answers. *—Kristin Leutwyler, staff writer*

PHOTOGRAPHS BY BETH PHILLIPS

SSRIs such as Zoloft (top), *Paxil* (middle) *and Prozac* (bottom) *help some women with severe PMS.*

The Female Orgasm

Women can reach orgasm through a wide variety of stimuli—including fantasy alone. So why do some women seldom or never experience the thrill?

by Evelyn Strauss, *special correspondent*

Meg Ryan's character demonstrated her prowess in faking an orgasm in the 1989 movie When Harry Met Sally.

We can only hope that when Sigmund Freud was developing his rigid notions of sexuality, some of his female contemporaries secretly knew better. As he sat in his study, weighing the merits of clitoral versus vaginal orgasms, these women might have been lying in their boudoirs, using fantasy alone to bring themselves to climax.

Women's bodies have long rejected stereotypical versions of sexuality, breaking many of the rules put forth by theorists and experimentalists. During the past several decades, researchers have been confirming that female arousal can take many routes. Despite the possibilities, many healthy and normal adult women have never experienced an orgasm, and many more do not achieve climax during intercourse. A woman can, however, enhance her sex life—with or without a partner—by letting her body's sensations guide her to paths that bring pleasure and ultimately, perhaps, orgasm.

The Genitals and Beyond

In their landmark study in the 1960s, sex researchers Masters and Johnson established some characteristics of the female physiological response to sexual activity. They found that during arousal, respiration, blood pressure and heart rate increase. Blood flows into the vagina and vulva, and the uterus rises as the upper part of the vagina balloons open. At orgasm, the outer third of the vagina, the uterus and other areas of the pelvic region contract involuntarily. According to Masters and Johnson, the clitoris, a small erectile organ near the front of the vulva, plays a central role in most women's arousal.

More recently, scientists have identified additional orgasmic pathways in women. For example, some women's vaginas contain a region of extreme sensitivity called the G spot. Stimulating this region—which lies on the front wall of the vagina—can produce great enjoyment and even orgasm in many women. "But it's important to realize that [the G spot] doesn't exist for all women," says social worker Kathleen Blindt Segraves of Case Western Reserve University. "You can have someone whose partner is really trying to find it, with no hope of success."

Some women also expel a fluid from their urethra when the sensitive area of their vagina is stimulated. Many find this intensely pleasurable, notes sexologist Beverly Whipple of Rutgers University. "We've been led to believe that there's only one way to respond sexually," she says. "There are women who felt that there was something wrong with them and had surgery to prevent fluid expulsion. But these are normal variations."

Additional routes to orgasm exist as well. Cervical stimulation provides intense pleasure for many women and orgasm for some. And some women can climax by stimulating parts of their bodies other than their genitals, such as their shoulders. "There are libraries full of material about the clitoris and the vagina and the G spot, but the rest of our bodies are also full of erotic potential," asserts Gina Ogden, a sex therapist in Cambridge, Mass. "I don't want to put this forward as a performance trip for women who are not orgasmic all over their bodies, but it's important to know the possibilities." More than half the women Ogden has surveyed say they have orgasms from extragenital touch, but these woman are probably rare.

Ogden also found that some women can reach orgasm without touching at all. Ogden, Whipple and behavioral neuroscientist Barry R. Komisaruk of Rutgers measured physiological changes such as blood pressure, heart rate and pupil diameter in seven women who could experience orgasm from genital self-stimulation or from fantasy alone. The researchers concluded that even if a woman arouses herself simply by thinking, the body can experience an orgasm that closely resembles one she brings about by touching her genitals.

Studies aimed at improving the quality of life for women with spinal cord injuries have suggested that diversity in orgasms extends to the underlying neurobiology as well. Women who have spinal cord injuries that are expected to block messages from the genitals to the spinal cord can still experience orgasms from clitoral, vaginal or cervical stimulation. These findings imply that additional neurological pathways lead to orgasm.

Obstructions to Climax

Despite the variety of methods by which some women can reach orgasm, many have never experienced one. Others don't reliably reach climax during sexual activity with a partner, although they can have an orgasm through masturbation.

Several studies and surveys—Masters and Johnson in the 1960s, the Hite report in the 1970s, the Chicago study in the 1990s and many others—have gathered information on sexual behaviors and functioning. The accuracy of the results suffers because the data were collected from nonrandom sampling and self-reports, but some general themes have emerged.

Researchers who study sexuality generally agree that between

5 and 15 percent of sexually active women have never had an orgasm. Furthermore, as many as 75 percent of women often do not have orgasms from intercourse, a percentage that surprises few in the field of sexology because most women require more direct clitoral stimulation than penile-vaginal sex provides.

Most commonly, nothing is fundamentally wrong with such women. Clitoral size, distance between the clitoris and the vaginal opening, and other anatomical variations do not correlate with the degree to which a woman is orgasmic, says social psychologist Clive M. Davis of Syracuse University.


EVERETT COLLECTION

Many factors, however, can hamper a woman's ability to achieve orgasm, including some diseases and medical interventions. When performing hysterectomies, for example, surgeons in the U.S. generally remove the cervix as well as the rest of the uterus to prevent cervical cancer. But the cervix is exquisitely sensitive in many women and can contribute to sexual pleasure. "In Europe, more supercervical hysterectomies [which leave the cervix intact] are done," says Sadja Greenwood, who teaches at the University of California at San Francisco. "Here women in the know are beginning to request [the technique], but it's not common medical practice." Some psychoactive and antihypertensive drugs also impede orgasm, as can hormonal disturbances.

If a woman is healthy and free from the known medical conditions that obstruct orgasm, the reasons she might not be able to reach a climax probably stem from psychosocial roots, points out clinical social worker Linda P. Alperstein of San Francisco. "But as we get more and more sophisticated in our knowledge about the chemicals in our body, we may find there are physiological factors that we hadn't considered at all," she says. "Depression used to be treated as a psychosocial phenomenon. Now we realize there's a strong biological component."

Most girls are immersed in negative and contradictory messages about sex as they grow up. "Societal credos and mythologies about how women should be have created all kinds of fears and beliefs that get in the way," Alperstein comments. "Women are taught that sex before marriage is bad, but after is good. They're told that women should be refined and should not let go. It's 'nice girls don't.' Sometimes women are still taught that they should be there for their partner's pleasure. They don't feel entitled to their own pleasure."

Freud's notion, for example, that women must overcome their desire for immature "clitoral" orgasms and move on to the more mature "vaginal" ones has led women to judge their orgasms. As a result, many heterosexual women hesitate to tell their partners that they like manual clitoral stimulation, for example, or intercourse in some arrangement other than the missionary position. These women might be ashamed that they can't have an orgasm like a "normal" woman—or they might fear bruising their partner's ego by implying that his lovemaking is inadequate.

"There are a number of women I see in therapy because they don't think they're having an orgasm the right way—not by intercourse alone, for example. That's the most frequent one," says Lonnie Barbach, a psychologist in San Francisco. Barbach encourages women to recognize the irrationality of the idea that one approach to orgasm is better than another.

Many women would like to have orgasms from intercourse alone, says Joani Blank, a sex educator in San Francisco. "This is a very deeply held desire on the part of many women. But whether we make a big deal about it or whether we let our partners beat us up emotionally because we don't [climax] that way is a whole other issue," she declares. "A woman can go through life thinking she's inadequate or she can say, 'So be it, this is how I am.' It might also be nice to be five foot nine."

Even if a woman feels comfortable having an orgasm from whatever stimulation works for her, distracting thoughts can interfere with the orgasmic process. "Women can be anxious or worried about taking too long or about their bodies," Barbach says. "Many things get in the way of allowing [women] to experience the pleasure that would lead to orgasm."

Quite often women become aroused but have trouble letting go. "Most of us want to look like the Mona Lisa instead of a gargoyle when we're having an orgasm, but the process is one of surrender," Alperstein observes. "Most of the time we try to fight against surrender—we try not to hit people when we're angry, try not to laugh too loudly, try to hide belly rumbles."

Anger, fatigue, stress and depression can also interfere with orgasm, although as with many of the other factors that get in the way, it can be difficult to separate the absence of libido from difficulty in climaxing. Previous traumas such as rape or sexual abuse sometimes pose barriers, too.

"But good sexual functioning is not a hallmark of good mental health, and problematic sexual functioning is not a hallmark of emotional problems," Alperstein says. "You can have trouble having orgasms for a wide variety of reasons other than serious relationship or psychological problems."

Wisdom of the Body

Some women need therapy to deal with the underlying issues preventing them from experiencing orgasm, whereas others can benefit from educational information and practice, Barbach maintains. For most women, the key lies in realizing that their bodies are the best teachers.

"The way for a woman to become orgasmic is to learn about her body through masturbation," says sexologist Betty Dodson of New York City. "Once she figures out what works for her, she can share that information with her partner." This approach boasts high satisfaction rates. Guided by a book or therapist, women participate in exercises that help them to discover what they like and dislike. They explore their attitudes about sex and are encouraged to use their imaginations as well as sexual aids to enhance arousal.

"Some women who have never experienced orgasm before find they can with the more intense stimulation provided by a vibrator," Blank reports. As they explore their bodies' responses and what kinds of fantasies augment their sexual experiences, most women eventually figure out how to bring themselves to orgasm. "The idea is to focus on pleasure, not achieving orgasm," Barbach says. The quickest route to orgasm, she suggests, is staying in the moment and simply following what feels good, not concentrating on a goal.

Even people who climax during masturbation can benefit from more practice. "You can work on losing the feelings of intense arousal and getting them back again so you realize it's okay when that happens with a partner," Barbach says.

But just as the routes to orgasm vary among women, so do the routes to sexual satisfaction. Not all women find orgasms necessary, and pressure to experience them can hinder a woman's sexual expression and enjoyment. "Some women have a wonderful time without orgasm," Alperstein states. "They like the intimacy and the closeness. What people feel good about is really very, very varied." SA

PHOTOGRAPH BY JAYNE WEXLER; HAIR AND MAKEUP BY LANA GERSMAN; BACKDROPS BY CHARLES BRODERSON

During their 30s and 40s, many women focus their health concerns on reproductive issues and raising a family. Of the approximately 42 million U.S. women in this age category, roughly one million gave birth last year.

30s and 40s

FACT SHEET

What women in their 30s and 40s need to know

According to the Centers for Disease Control and Prevention (CDC), in the U.S. 4,000 babies a year are born with spinal and other defects because of a **lack of folic acid,** or vitamin B_{12}, in the mother's diet. If a woman doesn't take in enough folic acid during pregnancy, birth defects can occur during the first few weeks of fetal development—often before the woman realizes she's pregnant. The U.S. Public Health Service recommends that women get 400 micrograms of folic acid in their diet or vitamin supplement each day regardless of whether they are trying to conceive. Most women between 19 and 34 get only 200 micrograms a day. Breakfast cereals, beans and **leafy green vegetables** are good food sources of folic acid.

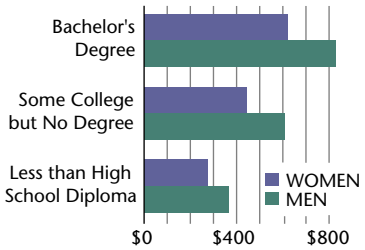
GREGG HADEL *Tony Stone Images*

In 55% of U.S. households, women contribute at least half the family income.

GEORGE CHAN *Tony Stone Images*

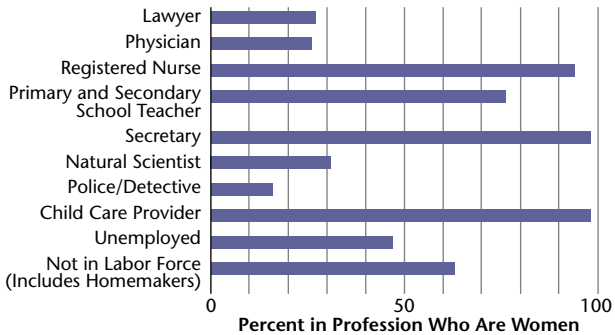
Do you experience an unpleasant burning sensation during urination? You could have a **urinary tract infection** (UTI), which is treatable with antibiotics from your doctor. UTIs result when bacteria from the vulva enter the urethra and travel upward to the usually sterile bladder or kidneys. One of the best ways to avoid a UTI is to urinate as soon as possible after intercourse to keep bacteria flushed out.

MEDIAN WEEKLY EARNINGS OF FULL-TIME WORKERS 25 YEARS AND OLDER



SOURCE: U.S. Bureau of Labor Statistics, 1997

WOMEN AT WORK



SOURCE: U.S. Bureau of Labor Statistics, 1997

Although the average age of menopause in the U.S. is 51, some women begin experiencing symptoms around age 40. If your monthly cycle extends to 45 days—or you experience hot flashes, night sweats and vaginal dryness—start keeping a calendar of your moods and symptoms. If they continue for three months, make a doctor's appointment and take your calendar. And find out when your mother went through menopause—chances are you'll be about the same age.

As your body ages, it becomes less efficient at absorbing the calcium you need for STRONG BONES. The National Institutes of Health recommends a daily dose of 1,000 milligrams of calcium for premenopausal women and 1,400 milligrams a day for pregnant women.

CHECKUP

Essential medical exams for women in their 30s and 40s

MAMMOGRAM

Although experts disagree on how often women should have mammograms, they do agree that surviving breast cancer depends on catching the disease in its infancy. Mammograms are x-rays of your breasts that can reveal cancerous growths or other abnormalities in breast tissue. The test is not perfect, however: mammograms sometimes yield false positives—indicating a malignancy where there really isn't one. An incorrect diagnosis of cancer can lead to tremendous stress and even unnecessary surgery.

The National Cancer Institute prescribes a mammogram once every one to two years for women over 40; the American Cancer Society (ACS) advocates an annual mammogram after 40. The American Medical Association (AMA) doesn't make a recommendation for women between 40 and 50 but suggests they consult their doctors (the AMA does endorse annual mammograms for women older than 50).

If you don't have health insurance to cover this test, call the ACS at 800-ACS-2345 to find the locations of low-cost mammogram clinics in your area.

COST: $50–$150

DIABETES TEST

If you are over age 40 and overweight or have a family history of diabetes, you should be screened for diabetes once every three years. Doctors diagnose diabetes by examining levels of glucose in your blood, which will be high if you are diabetic. Your doctor may also request a urine sample to check for the presence of ketones, chemicals that build up in the body if you're diabetic.

For more information, call the American Diabetes Association (ADA) at 800-342-2383 or visit the ADA at http://www.diabetes.org on the World Wide Web.

COST: Blood test $30–$50

54% of women older than 18 are married and live with their spouse. (U.S. Census Bureau)

TONY CORDOZA *Liaison International*

According to a United Nations survey of 152 countries, the U.S. is one of only six that does not have a national policy mandating paid maternity leave.

72% of women between the ages of 30 and 45 use some form of birth control. (National Center for Health Statistics)

BETH PHILLIPS

KEITH KENT *SPL/Photo Researchers, Inc.*

Staying healthy during pregnancy is very important—for both you and your baby. Consult your physician to develop a safe and effective exercise program. Aerobic exercise and moderate weight training are safe for most women, although you should be careful not to overexert yourself or overheat (your body temperature should not exceed 101 degrees Fahrenheit, or—easier to monitor at the gym—your pulse should not rise above 140 beats per minute). After your third month, stay away from exercises that require you to lie on your back—this position is dangerous because it can lower your heart rate and blood pressure as well as reduce blood flow to the baby.

PRENATAL TESTS

If you are pregnant, make a doctor's appointment as soon as possible to begin prenatal care for you and your baby. Your first visit will be a long one: you'll be asked for a detailed medical history, and your obstetrician will also perform a complete physical exam, including a pelvic exam and Pap test, and will check your blood pressure. He or she will take a sample of blood to determine your blood type and to test for conditions such as anemia, rubella and hepatitis B. Early in the pregnancy, you should be screened for sexually transmitted diseases and HIV.

After the initial trip to the doctor, your visits will be shorter. During the first six months of your pregnancy, you'll need to see your obstetrician about once a month; during months seven and eight, you should go in about once every two weeks. During the last month, you should see your doctor once a week until delivery.

Depending on your age and overall health, different tests may be necessary throughout your pregnancy. Mothers with a history of pregnancy problems, high blood pressure or diabetes may need multiple ultrasounds (in which the doctor looks at the baby in the womb using sound imaging) to monitor the fetus's growth and position and to check for physical abnormalities.

Mothers over age 35 often have an amniocentesis test, which involves extracting and examining a sample of the fluid that surrounds the fetus; the test can provide early indications of abnormal development. The American College of Obstetricians and Gynecologists suggests asking your doctor if the test is necessary for you.

Discuss with your obstetrician all the tests that are going to be performed. Be sure you understand why you're having the tests and what the risks are to you and your baby.

COST: Variable but usually covered by insurance.

SKIN EXAM

The American Cancer Society recommends that women older than 40 have a doctor examine their skin once a year for melanomas and fast-growing moles that could be signs of skin cancer.

COST: Included in a routine visit to the doctor.

PELVIC EXAM AND PAP TEST

The American Cancer Society suggests you schedule a pelvic exam once a year and a Pap test at least once every three years. Your gynecologist may recommend that you have a Pap test more frequently.

COST: Pelvic exam $40–$100; Pap test $20–$60. Usually covered by insurance.

UTERINE FIBROIDS EXAM

Prolonged menstrual periods, pelvic pain and frequent urination could be signs of uterine fibroids. Your doctor can check for these noncancerous growths during a pelvic exam.

COST: Included in a pelvic exam.

RECTAL EXAM

After age 40 a rectal exam should be performed with your yearly pelvic exam. Your doctor will inspect the wall between your rectum and vagina for abnormal growths and will check for polyps, hemorrhoids or blood in the rectum itself. Women who have a family history of colorectal cancer should talk to their doctors about any additional tests they should have.

COST: Included in a pelvic exam.

CHOLESTEROL TEST

The National Heart, Lung and Blood Institute (NHLBI) reports that a woman's cholesterol level often increases sharply between ages 40 and 60. Don't trust "finger-stick" cholesterol tests offered at work or the shopping mall—they are often inaccurate. To learn more about cholesterol and heart disease, visit http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm on the World Wide Web.

COST: $20–$35

DENTAL EXAM

Three out of four people older than 35 have some kind of gum disease. Visit the dentist regularly to have your teeth cleaned and examined for cavities.

COST: $60–$200

COMPILED BY STEPHANIE J. ARTHUR AND KRISTA McKINSEY; GRAPHS BY LAURIE GRACE

When the Body Attacks Itself

Autoimmune diseases afflict women much more frequently than men

by Denise Faustman, M.D., Ph.D.
Massachusetts General Hospital
and Harvard Medical School

Sex discrimination can happen anywhere—in the classroom, in the workplace and even inside the body. Take autoimmune diseases, for example: recognized autoimmune disorders afflict an estimated one in 20 Americans, but women can be 10 times more likely to develop clinical symptoms than men. Some 75 percent of rheumatoid arthritis sufferers are women. Similarly, women constitute between 70 and 80 percent of those with lupus (also known as systemic lupus erythematosus, or SLE) and between 80 and 90 percent of those with multiple sclerosis (MS). Why the gender bias?

The immune system normally works to defend the body against infections by identifying and eliminating invading viruses, bacteria and other disease-causing microbes. But in people with autoimmune disorders, the body turns on itself: the immune system mistakenly attacks other cells, tissues and organs. Why should a female's immune system be more prone than a man's to attack her own tissues? Or why should her tissues be more susceptible to autoimmune attack than a man's?

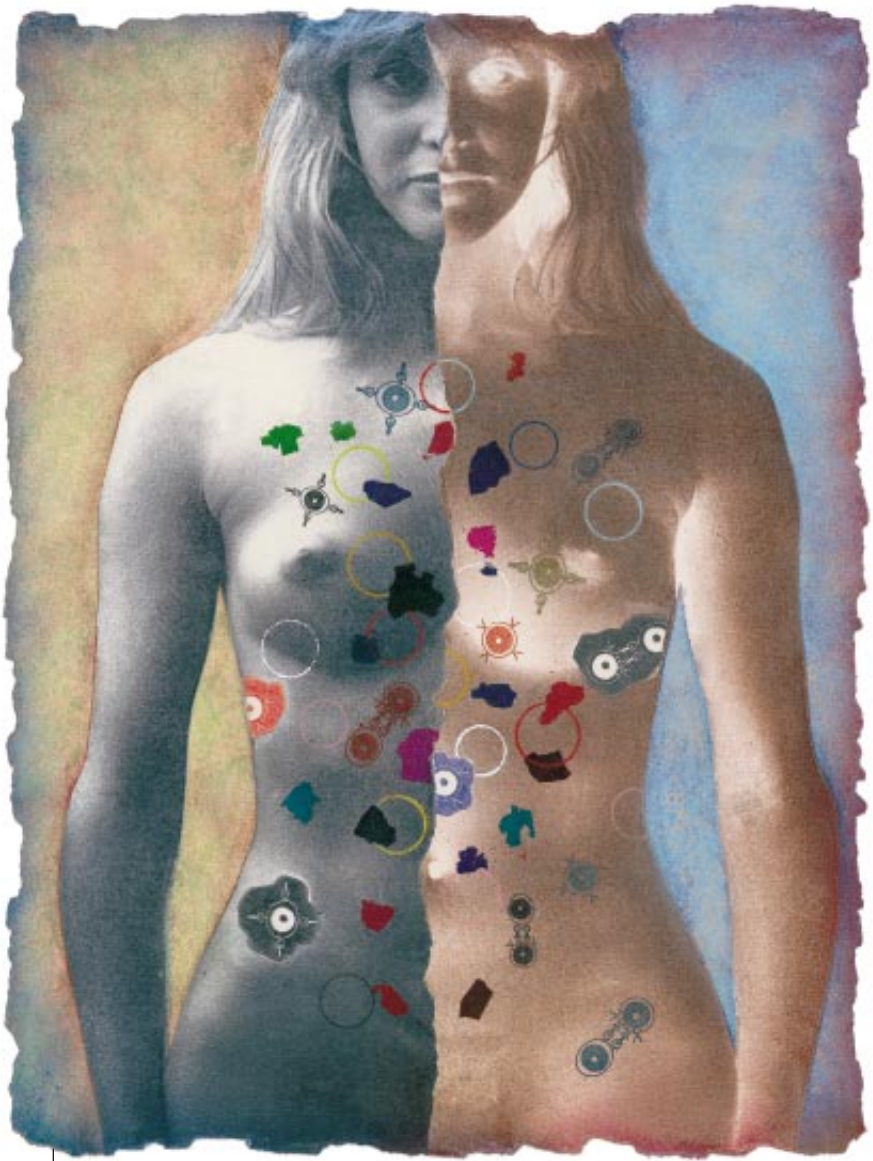
To address these questions, we need to understand more about how the immune system learns to identify which cells belong to the body and which are foreign. One of the key players is the T lymphocyte. These white blood cells, called T cells for short, police the body and attack any cells they recognize as foreign. Recent studies from my laboratory and others indicate that the process that normally instructs the T cells to differentiate between "self" and "nonself" may be flawed in people with autoimmune diseases. Further, it appears that the errors that hobble T cell training have different consequences depending on sex: males somehow circumvent the defects, which suggests that drugs based on male hormones may offer women some protection from the ravages of autoimmune diseases.

Autoimmune diseases attack a variety of tissues and organs in the body. In rheumatoid arthritis, the immune system targets the joints; in type I, or juvenile, diabetes, the insulin-secreting cells in the pancreas are attacked; psoriasis and vitiligo target the skin; multiple sclerosis and myasthenia gravis attack the nervous system; Graves' disease destroys the thyroid gland; Crohn's disease targets the gut; and diseases such as lupus, scleroderma and Sjögren's syndrome attack multiorgan systems, including the skin, joints, kidneys, lungs and heart.

Because autoimmune disorders are so diverse, the symptoms vary depending on the syndrome. Someone with rheumatoid arthritis usually experiences pain, swelling and stiffness in the joints, whereas someone with Crohn's disease experiences diarrhea and severe abdominal pain. But many of the autoimmune diseases—particularly lupus, type I diabetes and MS—begin with more nonspecific symptoms, such as fatigue, which can make them difficult to diagnose early on.

Anatomy of Autoimmunity

To help diagnose autoimmune diseases, physicians often use laboratory tests that detect autoantibodies. Autoantibodies are proteins, one of the major types of molecules that make up all cells, that are mistakenly produced by the immune system and that recognize the body's own tissues. (In contrast, regular antibodies recognize only invaders.) At present, there are no cures for autoimmune disorders. Treatment involves using anti-inflammatory medications such as acetaminophen or ibuprofen to control the pain and, if the disease is severe, immunosuppressive drugs such as prednisone or cyclosporine to dampen the activity of the immune system. Unfortunately, immunosuppressive drugs prevent T



J.W. STEWART

In women (and men) with autoimmune diseases, immune cells that normally protect the body from infection attack the body instead.

cells from multiplying, thereby hampering the immune system's ability to fight off infections, an effect that causes problems on its own. Although the various autoimmune diseases present different clinical pictures, they share a fundamental biological cause: T cells that destroy other cells of the body as if they were invaders.

Attack of the Killer T Cells

As part of the body's defense team, T cells patrol the bloodstream and tissues searching for any foreign proteins that might signal an infection. Early in their development, T cells must learn to recognize which proteins might be foreign and which are normal cellular proteins. In infants the training process centers in the thymus (hence the name T cells), an organ that lies between the lungs near the top of the breastbone. But T cell education continues in the bloodstream throughout a person's life. T cells are taught to distinguish between self and nonself throughout the body by specialized immune cells called antigen-presenting cells.

Antigens are bits of protein that can invoke an immune response. Antigen-presenting cells expose T cells to protein fragments that come from invading bacteria and viruses and teach them to attack whenever they encounter such foreign proteins. This process primes T cells to destroy any cells in the body that might be infected by a disease-causing virus or microbe. But antigen-presenting cells also display fragments of proteins derived from the body's own cells. In this case, the antigen-presenting cells train the T cells to ignore healthy cells that are part of the body. Normally, any T cells that show a tendency to attack cells that are displaying self-antigens are quickly eliminated.

In 1991 my colleagues and I determined that the antigen-presenting cells in patients with type I diabetes are not adequately educating T cells to distinguish between foreign antigens and self-antigens. The antigen-presenting cells fail to present protein fragments properly for T cell inspection—a sign of cellular immaturity. Since then, we have discovered that people with many different autoimmune diseases possess a similar defect in antigen presentation. Patients with lupus, rheumatoid arthritis and MS all possess immature antigen-presenting cells. Such immaturity may hold the key to autoimmune disease. If antigen-presenting cells are immature and do not properly display self-antigens, they can fail to instruct T cells to leave the body's tissues alone. Ours was the first evidence in humans to suggest that the fault lies not in the T cells but in their teachers.

Finding the Defect

Why don't antigen-presenting cells mature in people with autoimmune disorders? To answer that question, we turned to an animal model of autoimmune disease, the nonobese diabetic (NOD) mouse. These mice develop symptoms of several different autoimmune diseases, including diabetes and Sjögren's syndrome. And like humans with autoimmune disease, NOD mice have immature antigen-presenting cells that fail to teach T cells to recognize the body's tissues. When we examined female NOD mice—80 to 90 percent of which exhibit signs of autoimmune disease—we found that the animals had a defect in their antigen-processing pathway. Before antigen-presenting cells can display protein fragments for T cell inspection, they have to process them internally. This involves cutting up the proteins into the right-size fragments and shipping them to the surface of the antigen-presenting cell, where the T cell can find them easily.

By 1997 my colleagues and I had found that NOD mice have a single mutation that effectively cripples antigen processing in antigen-presenting cells. The defect actually shuts down two genes that are critical for antigen processing and the maturation of lymphocytes, including T cells. When these genes are inactivated by mutation, antigen-presenting cells don't mature as they should,

and they fail to display properly the protein fragments that teach T cells what to attack—and what not to attack. Although people with autoimmune disorders also have impaired antigen processing, we have not yet linked mutations in the human versions of these defective mouse genes with a human autoimmune disease. Even if such mutations were found, autoimmune diseases are very complex and will probably involve problems in multiple genes. Although no single mutation is likely to underlie all autoimmune diseases—or even any particular one—each new discovery could point the way toward more effective treatments for these disorders.

What about Sex?

NOD mice show the same kind of gender bias as humans when it comes to developing symptoms of autoimmune disease. Although the mutation we discovered is present in both male and female NOD mice, only 10 to 15 percent of male NOD mice develop diabetes. So how could this defect hamper the maturation of antigen-presenting cells and antigen presentation preferentially in females, leaving males largely unaffected? Most male mice seem to be able to get around the mutation and generate enough mature antigen-presenting cells to avoid disease.

We suspect that hormones somehow play a role in sparing males from the harmful effects of this mutation—or in condemning females to experience them. But we are not yet sure which hormones are involved. Is testosterone protecting males from the potentially deleterious effects of the NOD mutation? Or do female hormones, including estrogen, somehow aggravate the condition in females? In NOD mice, experimental evidence suggests that testosterone could have protective effects against diabetes. Years ago researchers found that castrated male NOD mice increased their incidence of autoimmune disease. Moreover, the scientists found that giving testosterone to females actually diminished their development of disease. How testosterone could have such an effect is not known.

The clinical picture in humans is more complex. For many of the autoimmune disorders, females do not experience symptoms until they reach puberty, again suggesting that hormones play a role. But for juvenile type I diabetes, onset usually occurs before puberty. And some women with MS do not experience symptoms until after menopause. Observation of women with autoimmune disorders suggests that fluctuations in hormone levels—during menstruation and pregnancy—can either exacerbate or alleviate their symptoms. Women with rheumatoid arthritis often go into complete remission during pregnancy, a time when estrogen levels are high. Yet patients with lupus rarely experience remission of symptoms during pregnancy. In fact, early studies reported that pregnancy could cause disease flare-ups in women with lupus.

It is also possible that other factors unrelated to female hormones can improve or worsen autoimmune symptoms in women. In the case of pregnancy, the presence of foreign fetal cells in a woman's body suggests at least an altered state of immune recognition. And the effects can last much longer than just nine months. Recently researchers at the Fred Hutchinson Cancer Research Center and the University of Washington found that after pregnancy, women with scleroderma had fetal cells circulating in their blood more frequently and in higher numbers than healthy mothers did. Fetal cells often escape from the uterus and circulate through a mother's bloodstream, sometimes for decades after a pregnancy. Perhaps such foreign cells might somehow antagonize normal immune system function. On the other hand, their presence might be a result of immune system dysfunction, rather than a cause.

Little Pink Pills?

Autoimmune disorders are not the only maladies to display a gender bias: heart disease, for example, affects many more men than women. Studies have shown that estrogen, to some degree, protects premenopausal women from heart disease—a major reason why menopausal women often choose to go on estrogen therapy. Even men who are at risk for heart disease might benefit from taking drugs that mimic estrogen's heart-protecting effects.

So why not develop an equivalent treatment for women with autoimmune disease? Scientists in the pharmaceutical industry could design a drug that has the protective properties of testosterone but lacks its masculinizing side effects. Such studies are not yet being done, perhaps because clinical trials for chronic disorders such as autoimmune diseases are expensive and take many years to complete. Further, because many of the autoimmune diseases remit and relapse spontaneously, it is difficult to tell when recovery is the result of a specific therapy. Five years ago, when the Food and Drug Administration approved beta-interferon (a drug that alleviates the progression of MS by an unknown mechanism), it was the first new drug approved to treat autoimmunity in 20 years.

Some postmenopausal women now take testosterone to increase their sex drives, but there are no data indicating whether any of these women had autoimmune disorders—or whether the testosterone alleviated their symptoms. To be most effective for treating autoimmune diseases, such drug therapies would need to be initiated before the disease is full-blown—at birth, if possible. By screening blood samples for autoantibodies, physicians can identify children who are one year old, or maybe younger, at risk for juvenile diabetes.

Beyond Genes

If all the autoimmune diseases are caused by the same—or similar—genetic and cellular disruptions, why does diabetes destroy the islet cells of the pancreas, whereas MS attacks the nervous system? It appears that the affected tissues themselves may become more susceptible to autoimmune attack. Tissues such as the pancreas that secrete hormones might produce and release antigens that attract the attention of marauding T cells. Further, such target tissues might be weaker and less able to defend themselves against T cell attack than other tissues. In the future, we may understand better how mutations in the various genes that control antigen processing might interrupt the development of the immune system in women with autoimmune diseases. And we would like to determine exactly how most men are protected from the deleterious effects of these mutations.

In the meantime, these studies should give hope to people, particularly women, with autoimmune disorders. The results suggest that even when a defective gene prevents the immune system from fully maturing, the proper drugs might be able to change the course of the disease. If we can learn how most males avoid autoimmune disorders, females, too, may one day be spared. SA

DENISE FAUSTMAN is director of the Immunobiology Laboratory at Massachusetts General Hospital and associate professor of medicine at Harvard Medical School.

Are Autoimmune Diseases Colorblind?

Do autoimmune disorders discriminate on the basis of race, as well as sex? In the case of lupus (systemic lupus erythematosus, or SLE), the numbers are fairly striking: the disease is three times more common in the African-American population than in the Caucasian population. Lupus affects approximately one in 300 African-American women and one in 1,000 white women over the age of 18.

Type I diabetes and multiple sclerosis, on the other hand, appear to be more common among Caucasians than African-Americans, Native Americans or Hispanic-Americans. And rheumatoid arthritis is found in all races, with certain Native American populations having an increased incidence, says Elaine Collier of the National Institute of Allergy and Infectious Diseases.

Making definitive statements about the effects of race on autoimmune diseases, it turns out, is by no means easy. "Each disease is different," Collier remarks. "There's not really any overriding theme, except that genetics seem to play a role in determining risk." So researchers tend to focus on a single disease as they try to tease apart the genetic and environmental factors that may influence disease incidence and outcomes and try to determine whether race, on its own, has any effect on who gets the disease and how it will affect an individual's health.

Understanding the factors that contribute to the development and progression of autoimmune diseases should help researchers develop more targeted and rational treatment protocols. The first part of the problem is confirming that racial differences exist. "Getting statistics on how many people have each disease is hard," Collier comments. "Based on that, it's harder to say how many people in any particular race have the disease." The nature of autoimmune diseases also makes them difficult to pin down, statistically speaking. "For good epidemiological studies, you need a very large number of cases, and these are rare diseases," points out Marc C. Hochberg of the University of Maryland. And to study race, the population must be sufficiently diverse. "The Mayo Clinic in Minnesota has a good database [of patient information]," Hochberg says, "but the population is almost 100 percent Caucasian."

Many studies rely on data collected from medical centers in and around large cities, such as Baltimore, Pittsburgh, Boston or New York, states C. Kent Kwoh of Case Western Reserve University and the Veterans' Affairs Medical Center in Cleveland. In 1995 Kwoh (then at the University of Pittsburgh Graduate School of Public Health) and his colleagues reviewed medical records obtained from area rheumatologists, hospitals and the Pittsburgh Lupus Databank and confirmed that the incidence of lupus in African-American females is three times higher than in white females. But that study, reported last year in the journal *Arthritis and Rheumatism*, is just the "tip of the iceberg," Kwoh says. "First we had to document that there are racial differences. Now we need further studies to find out why those differences exist."

One factor that certainly influences the course of any disease is the patient's socioeconomic status. "It's been known for centuries that being poor is bad for your health," observes Matthew H. Liang of Harvard Medical School. "But knowing that isn't really helpful: we can't eliminate poverty." So Liang and his colleagues set out to identify the "modifiable" factors related to socioeconomic status that might contribute to the severity of lupus.

The researchers collected information from 200 patients with the disease, including each person's race, age at diagnosis, socioeconomic status, diet, compliance with treatments and access to health care systems. Their conclusions? The researchers reported last year in *Arthritis and Rheumatism* that when they compared patients who were in the same socioeconomic class, none of the outcomes they measured, including health status and degree of organ damage, were associated with race. Instead the patients who fared the worst, healthwise, were those who were least able to handle their disease—by taking care of themselves and feeling confident that they could deal with disease flare-ups, for example.

Such studies offer hope, says Hochberg, who also works on lupus, because the risk factors that appear to be highly correlated with the progression of lupus are under the patient's control. With better education and adequate access to health care providers, patients can learn how to comply with their treatment protocols, eat healthier diets and generally take charge of their disease—changes that should help improve their condition, regardless of race.

So where do the differences between African-Americans and Caucasians come from? Collier and other researchers assert that genetic differences might influence the susceptibility, onset and progression of autoimmune diseases in different races. "Genetics reveals first principles," says John B. Harley of the University of Oklahoma and the Oklahoma Medical Research Foundation. "The genetic differences between individuals constitute why one person will get a disease and somebody else won't."

Harley is currently coordinating the identification of families in which more than one family member has lupus for a nationwide Lupus Multiplex Registry and Repository. So far he has contacted and collected DNA samples and clinical information from 1,000 individuals in 160 different families. Using these samples, Harley and his colleagues hope to identify genes that might be involved in lupus. At the American College of Rheumatology conference last winter, the researchers reported identifying a region on chromosome 1 that appears to correlate with lupus in African-Americans but not in Caucasians. The region contains many genes involved in the immune response, and the investigators still have quite a bit of work to do before they can identify which gene in the area is involved in lupus.

Others searching for lupus genes have also wound up studying chromosome 1. One of these genes appears to correlate with a high incidence of lupus nephritis—loss of kidney function—which occurs more frequently in African-Americans with lupus than in whites. Another genetic region appears to play a role in lupus in African-Americans, Asians and Caucasians, suggesting that the biological basis of the disease might be similar for different races.

In the end, such studies will help define the subtle differences that might exist in the way that people of different races acquire disease—why they get it, how they respond to treatment and how the disease progresses. Armed with this knowledge, scientists should be able to design more effective therapies for treating all people who have autoimmune disorders.

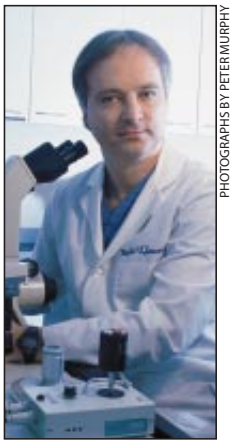
—Karen Hopkin, special correspondent

For more information on autoimmune diseases, contact:
American Autoimmune Related Diseases Association at 800-598-4668 or at http://www.aarda.org on the World Wide Web.
National Institute of Allergy and Infectious Diseases at 301-496-5717 or at http://www.niaid.nih.gov/publications on the World Wide Web.
National Institute of Arthritis and Musculoskeletal and Skin Diseases at 301-495-4484 or at http://www.nih.gov/niams/healthinfo/ on the World Wide Web.
National Institute of Diabetes and Digestive and Kidney Diseases at 301-654-3810 or at http://www.niddk.nih.gov on the World Wide Web.

Q&A

Infertility

Zev Rosenwaks, M.D.



PHOTOGRAPHS BY PETER MURPHY

Mark V. Sauer, M.D.

Since 1978, when the first test-tube baby was born, infertility treatments have become widespread. Today 315 fertility clinics operate in the U.S., offering infertile women and men an array of expensive, high-tech procedures with acronyms like IVF (in vitro fertilization), GIFT (gamete intrafallopian transfer) and ICSI (intracytoplasmic sperm injection). Aided by IVF and other procedures, 72,000 babies have been born in the U.S., according to the American Society for Reproductive Medicine, and about 15 percent of American women have sought some type of infertility treatment. The increasing demand for infertility treatments has been partly spurred by the aging of the baby boom generation. About 6.1 million women in the U.S., or 10 percent of the women of reproductive age, are now infertile, compared with 4.9 million in 1988, as reported by the National Center for Health Statistics.

Nearly every advance in the treatment of infertility generates ethical dilemmas and controversy. Two pioneers in the field are **ZEV ROSENWAKS, M.D.,** *professor of obstetrics and gynecology and director of the Center for Reproductive Medicine and Infertility at New York Hospital–Cornell Medical Center, and* **MARK V. SAUER, M.D.,** *professor of obstetrics and gynecology at Columbia University and director of reproductive endocrinology at Columbia-Presbyterian Medical Center. In the following interview,* **MARJORIE SHAFFER,** *special correspondent for* SCIENTIFIC AMERICAN, *talks to these doctors about the latest advances and dilemmas in the treatment of infertility.*

Q *What are the most common causes of infertility today?*

A **ROSENWAKS:** That depends on the demographics in the area that a fertility clinic serves. In our clinic, the most common reasons are male infertility caused by problems with a man's sperm or female infertility caused by endometriosis, ovulatory dysfunction and advanced maternal age.

SAUER: Age-related infertility is an increasingly common reason women seek fertility treatments. Ten years ago maybe 5 percent of my patients were around the age of 40; today probably 80 percent of my patients are between the ages of 40 and 50. Many of these women have nothing wrong with them, except that they are older. The likelihood of a successful pregnancy in a woman over the age of 45 using her own eggs is very low. But using donor eggs, success rates are unaffected by age: women over the age of 45 have the same likelihood of giving birth as 35-year-old women. According to registry data from the Society for Assisted Reproductive Technology, since 1990 there has been more than a 10-fold increase in the number of women over 40 receiving IVF and a nearly 10-fold rise in the number of egg donations.

Last year Reproductive Biology Associates (RBA), a fertility clinic in Atlanta, reported that a woman gave birth to twin boys conceived with donor eggs that had previously been frozen. Is this a breakthrough? How will it affect the treatment of infertility?

ROSENWAKS: Ethically, it is much more acceptable to freeze gametes—eggs and sperm—than embryos. We do freeze eggs for women who have cancer and will undergo chemotherapy, but we tell them this is far from an efficient procedure. There is no guarantee that we can preserve their ability to reproduce. One needs to put this latest news of egg freezing, as encouraging as it might be, into perspective. The chances of achieving a pregnancy with each previously frozen egg is probably no greater than 2 percent. This is still an area that requires further refinement. I hope healthy young women don't see egg freezing as a convenient way to bank their eggs for use 20 years later.

SAUER: I think the Atlanta births promise to be a big breakthrough. We have been approached by two sets of patients who want to freeze their eggs. The first are women who are ill and want to preserve their reproductive capacity because treatments

like chemotherapy damage the ovaries. The second are professional women in their mid-30s who are becoming aware of the reproductive hazards of aging and have no desire to bank embryos but think they might want to use their eggs later with a husband or boyfriend. Despite the demand, many eggs never survive the freezing process. The good news is that along with RBA, two groups in Italy have had successful pregnancies using previously frozen eggs. So I think we will continue to improve the technology, and eventually it will become commonplace.

Making Parents

Assisted reproductive technologies have enabled women well past menopause to give birth to children conceived with donor eggs. Is there an age beyond which a woman can no longer give birth?

ROSENWAKS: Theoretically, it is possible for a 70-year-old woman to have a baby. But we have a responsibility to safeguard the health of the woman and her baby. Nothing is guaranteed in life, but is it fair for a child to be born to a couple in their 70s? How long will that child have with his or her parents? We usually only treat women of reproductive age, meaning up to the age of menopause.

SAUER: I have treated well over 100 women in their 50s, and they have done extremely well, even those who gave birth to triplets. But it is a very biased cohort of patients; they are very healthy. We usually won't treat women over the age of 55 unless there are compelling reasons. In the last year we had three women over that age: they were 57, 59 and 61. The two women in their 50s already had babies through IVF in my practice and wanted another child. These women were healthy, and I saw no reason not to help them again. And what was the compelling reason for the 61-year-old woman? Well, she lied about her age. We thought she was quite a bit younger. When a woman over the age of 55 comes to see me, our department's ethics committee and many other staff members discuss the merits of her particular case. If a woman older than 55 has survived cancer, for example, and she couldn't conceive when she was younger because she was getting treated for cancer, we would probably treat her, if she understands the risks.

Some reproductive immunologists contend that some women have repeated miscarriages because they produce antibodies that interfere with the growth of the placenta or the embryo. These specialists say that aspirin, the anticoagulant heparin and intravenous immunoglobulins can counteract such antibodies. Do such immunotherapies offer hope to childless couples?

ROSENWAKS: There is compelling evidence that genetics plays an important role in IVF failure, but it is difficult to understand how immunological rejection does. In our clinic, we get very high pregnancy rates without immunological treatments. There is no doubt, however, that in specific cases you can demonstrate an immunological reason for miscarriage. But one needs to be careful to tailor treatment to the findings. You have to be cautious; immunotherapies have to be tested in clinical trials. In our hands, at least in preliminary work, we have administered heparin or aspirin—both of which can prevent clotting abnormalities in developing embryos and are considered immunotherapies—to women for whom IVF has failed, and we haven't observed that the drugs have made any contribution to the success or failure of IVF.

SAUER: Immunotherapy is a very controversial field. If you look at a well-defined population of women who have had recurrent miscarriages, there is certainly a subgroup that has persistently high levels of antibodies. But the panels of tests for detecting these antibodies are very expensive, and immunotherapies aren't innocuous, making it harder and harder for patients and their physicians to know what to do. We have had some success with the therapies, but they are still not proved in clinical trials.

Some researchers believe that many cases of male infertility are the result of genetic defects and that ICSI might promote the transmission of these defects by allowing defective sperm to fertilize an egg. Is this concern warranted, and how it is being addressed?

ROSENWAKS: There is a higher frequency of genetic deletions in the Y chromosome that may or may not be associated with infertility in men with severe oligospermia, or below-normal sperm counts. Sons conceived with the aid of ICSI will have the same genetic abnormality as their fathers. We recommend that all men with severe oligospermia undergo genetic testing; about 10 percent will have deletions or other chromosomal abnormalities. These aren't lethal defects. Men often tell us, "Well, I have it, so the worst that will happen is that my son will have it." But men who have a congenital absence of the vas deferens, the duct that carries semen from the testes, also carry the gene for cystic fibrosis. Before implantation into the uterus, we recommend genetic testing of all embryos conceived with the sperm of men who lack the vas deferens. This is an important area of investigation because these men can transmit the cystic fibrosis gene to their children.

SAUER: Men who are sterile or subfertile might carry deleterious genes that through natural selection wouldn't be passed on. We now know that 5 to 15 percent of infertile men have definable Y chromosome deletions associated with infertility.

The ABCs of ART

(Assisted Reproductive Technology)

IVF In vitro fertilization. Eggs are removed from a woman's ovary and are fertilized by a man's sperm in the laboratory. The resulting embryos are then transferred into the woman's uterus. The procedure is used in some 70 percent of assisted reproduction procedures, according to the latest statistics available from the U.S. Centers for Disease Control and Prevention (CDC).

ICSI Intracytoplasmic sperm injection. One sperm is injected directly into an egg in the laboratory to achieve fertilization. The embryo is then transferred into the uterus. The technique has been used since 1992 to conquer the problem of low sperm counts, sperm with little movement or sperm that cannot penetrate an egg. According to the latest CDC statistics, roughly 11 percent of assisted reproduction procedures include ICSI.

GIFT Gamete intrafallopian transfer. Eggs are removed from a woman's ovary and are placed, along with sperm, into the woman's fallopian tubes, where fertilization takes place. GIFT is used in only 6 percent of assisted reproduction procedures, as reported by the CDC. —*M.S.*

Perhaps these deletions are linked to other disorders yet to be unmasked that will become more common as generations of ICSI-conceived sons are born. There are places in the world, like the Netherlands, where ICSI has been put on hold because they want to have a national debate before they initiate care. The good news is that to date there doesn't appear to be an increase in pregnancy loss or chromosomal abnormalities affecting sons conceived through ICSI. But these children are young. We would be more reassured if we followed these children for 20 years and there still wasn't an increase in abnormalities.

Will it ever be possible for a man who produces no sperm at all to father a child?

ROSENWAKS: Yes. I think that in the future we may be able to create a spermlike cell from a normal body cell by using cloning technology. This would be a different process than the one used to make Dolly the sheep. Everybody talks about how cloning shouldn't be done to make an identical individual, and we agree. But—and this is just speculation—let's say that you could take a normal body cell from a man and transplant it into an egg that had had its nucleus removed and induce it to divide in such a way that the resulting cells would have only half the number of chromosomes as the original cell, like sperm and eggs. These cells could be used to fertilize an egg through IVF. I think this use of cloning technology is much more akin to natural reproduction. The transformed cell would undergo recombination, or genetic reshuffling, the same way as any sperm cell, and therefore this process would be devoid of the potential social and biological risks of cloning.

Risks and Trade-offs

The use of fertility drugs in assisted reproduction has led to an enormous rise in the number of multiple pregnancies because many embryos have to be put into a woman's uterus to ensure a successful pregnancy. What strategies—besides selective abortion of one or more embryos—are being developed to improve the chances that only one child will be born as a result of IVF and other assisted reproductive technologies?

ROSENWAKS: Theoretically, if you could identify the embryo in the laboratory that has a high likelihood of implantation, then you could transfer one, at most two, embryos. If you could nourish embryos in improved media and grow them in the laboratory with the cells that embryos ordinarily encounter in the uterus, then you could transplant the embryo into the uterus when it is five days old, when it has the best chance of implanting. We have established a system where we use the mother's own endometrial, or uterine lining, cells previously obtained during a natural menstrual cycle.

SAUER: This is an avant-garde area of research. The reasons we transfer multiple embryos at 48 or 72 hours of age relate to the culture media and laboratory conditions, which have always been suboptimal. It becomes more perilous for the embryo after two or three days. But if we can delay the implantation until the embryo is five days old, when it is more developed, then we could transfer only two or three embryos into the uterus. At that stage of development, embryos have the best chance of implanting. We are working on a strategy called staged culture media, in which the technician changes the culture medium as the embryo gets further along, allowing the embryo to grow more efficiently to the five-day stage.

Assisted reproduction is an expensive process. One cycle of IVF costs $8,000, and most insurers in the U.S. won't cover the cost. What is needed to bring the cost down to more affordable levels?

ROSENWAKS: Society and government should look at IVF as a practical, efficient way of treating the important medical problem of infertility. And the government should fund research and development in this field so that these costs will not be added to the cost of IVF. IVF is a labor-intensive endeavor, however; you don't just perform surgery for an hour. You treat the patient for three weeks to a month at a time; the patient has multiple blood tests and ultrasounds and has eggs retrieved. These procedures require many nurses, technicians, embryologists and physicians. This is expensive. But if you look at the cost efficiency per baby, IVF in properly selected patients is probably less expensive than other treatments for infertility. Consider a woman who has undergone surgery to remove blockages in her fallopian tubes. If that surgery doesn't solve her infertility problem, then she and her husband may wish to try IVF, which can lead to the birth of a child. If you compare the cost of the surgery and IVF, then IVF would be more cost-effective.

SAUER: I would prefer to see universal coverage for infertility. But the question is, Who will pay for it? There is little that will keep these costs down; if anything, the costs will continue to rise. There is a lot of money being made. It isn't just physicians who drive this, but pharmaceutical companies as well, which have continually raised the price of their products to whatever the market will bear. To me, it is sort of a sad commentary on this field of medicine. The field is becoming a lot like plastic surgery—whoever can afford it will get it. We have fought government regulation, believing that physicians should regulate themselves. But I am concerned now that we are just kidding ourselves. I am starting to rethink whether it is time for the federal or state governments to say enough already, let's figure out a way to get patients the treatments they need in a cost-effective, reasonable way.

It seems that most infertility treatments involve medical procedures for the woman, even if it's the man in the couple who's infertile. Why isn't more known about male reproductive biology?

SAUER: This is a valid question. Is there sexism being practiced in this field? I think there is. Perhaps women are more willing to endure the probing, sticking and general invasiveness of many infertility-treatment procedures. Most men would never put up with it. The male reproductive system also is a lot more redundant than a woman's. There are millions, if not billions, of sperm, and you can have an awful lot wrong with a man's anatomy and physiology and he can still father a child. Nature is less forgiving to women.

Has there been any long-term follow-up of the thousands of children born worldwide with the aid of assisted reproductive technologies? Are these children more likely to have certain health problems?

ROSENWAKS: More than 4,300 children have been conceived through IVF just in our clinic alone. In the small studies that have looked at children at one to two years of age, IVF had no deleterious impact on their general health and intelligence. No matter what you do in medicine, it is desirable to follow up on the consequences of any procedure. But there have been hundreds of thousands of babies born through IVF, and I don't

think there is any reason to believe that there would be long-term health problems in these children.

SAUER: I don't think there are any large population studies of IVF-conceived children, and there is a good reason for that. A lot of people have gone through such hell to have a child this way, and they are so relieved not to have to think about it anymore that they are not too compliant in follow-up studies. Most of the studies have been done in young children, and there doesn't appear to be anything different about these families, other than a lot of multiple births. When you get triplets in a family, there are a lot of unique stresses. But I don't think there is much to be concerned about. SA

Endometriosis: A Major Cause of Infertility in Women

Some women experience severe abdominal pain, nausea, vomiting, bloating, and heavy or irregular bleeding during their periods. For others, the only symptom is infertility. Still others have terrible cramping pains during their periods but can become pregnant readily.

The problem all these women share is endometriosis, a disease of the reproductive system that is largely a mystery despite the fact that it afflicts between 3 and 10 percent of all women of reproductive age. But despite its prevalence, many women with endometriosis remain undiagnosed because there are no biochemical markers for the disease that can be detected in the blood or urine.

Researchers are now looking for the cause of endometriosis, which renders between 30 and 40 percent of the women who have it infertile. Understanding the cause will allow better diagnosis and treatment.

Endometriosis occurs when the tissue lining the uterus, which is called the endometrium, detaches itself and takes up residence in the abdomen outside the uterus, perhaps by traveling up through the fallopian tubes. This roving (endometriotic) tissue usually plants itself near the ovaries, on the outer surface of the uterus, in the cul-de-sac behind the uterus and in the area between the vagina and the rectum. The growths can also be found on the outside of the fallopian tubes; on abdominal surgery scars, the intestines and the bladder; and even in such far-flung places as the lungs, arms and brain.

The pain of endometriosis results because the transplanted tissue continues to swell and bleed in response to the same hormonal cues as normal endometrial cells during the menstrual cycle. But, unlike the normal cells, which are flushed out of the body each month during menstruation, the transplanted tissue has no place to go—it remains inside the body, causing adhesions, inflammation and scarring.

Many questions about endometriosis remain unanswered. Researchers still don't know why some women with mild endometriosis are able to get pregnant while others can't. Severe endometriosis is easier to understand: infertility occurs because the fallopian tubes are blocked or the ovaries have sustained damage.

"This is such an enigmatic disease," says Sandra A. Carson, professor of obstetrics and gynecology at Baylor College of Medicine. "Pain and other symptoms may not correlate at all with the size of the endometrial growths. We need to understand the stages of this disease and their association with molecular signals. And we need to have a marker in the blood that we could use to diagnose this disease."

Although no one theory can account for all cases of endometriosis, in the late 1980s the notion that retrograde menstruation is a cause of the disease gained supporters. According to this theory, menstrual tissue backs up through the fallopian tubes during menstruation and into the abdomen, where it adheres and proliferates.

Yet of the 75 to 95 percent of all women who experience retrograde menstruation, only some develop endometriosis. "In the past, we hypothesized that there must be something wrong with the immune system of women who develop a disease that allows transplanted endometriotic cells to grow outside the uterus," says Serdar E. Bulun, professor of obstetrics and gynecology at the University of Texas Southwestern Medical Center at Dallas. "But then we started to ask whether there was something distinctly different in the transplanted tissue itself that allows endometriosis to develop."

Once researchers turned their attention to the transplanted endometriotic tissue, they began discovering many differences between the transplanted cells and normal cells. Some groups have found increased concentrations of inflammatory proteins and other components of the immune system in the transplanted endometriotic cells, whereas others have identified proteins that might uniquely identify the cells.

These findings may lead to new therapies and to diagnostic markers in the blood. Currently the only way to diagnose endometriosis is through laparoscopy, a surgical procedure in which the abdomen is viewed through a tubelike instrument with a light attached.

Some of the recent findings about endometriotic transplants are leading to novel ideas about how the disease occurs. Bulun and his colleagues, for example, have detected high levels of an enzyme called aromatase in the transplants. Aromatase is a key player in a series of reactions leading to the production of the hormone estrogen, which can sometimes provoke endometrial cells to proliferate and cause cancer.

Bulun's group has found that aromatase levels in transplanted endometriotic tissue are as high as levels of the enzyme in the ovaries, where estrogen is produced. "This transplanted tissue is devious enough to make its own estrogen," he says. "The estrogen is like fuel. If you cut the supply, the tissue will stop growing."

Bulun speculates that hormonelike chemicals called prostaglandins, which are found in the abdominal cavity and elsewhere, cause aromatase in transplanted endometriotic tissue to go into overdrive and produce more estrogen. Prostaglandins play a wide variety of roles but are implicated in many of the symptoms of endometriosis, especially pain.

Traditional treatments for endometriosis, such as the drug danazol or gonadotropin-releasing hormone agonists, inhibit the production of estrogen in the ovaries. But Bulun says some women with severe endometriosis don't respond to these treatments, because the drugs don't stop estrogen production in endometriotic transplants outside the uterus. His group is developing aromatase inhibitors that might become new treatments for the disease.

Still, some researchers doubt there will prove to be a single magic bullet for endometriosis. "We have lots of abnormal findings, and it isn't clear which of them is the cause and which the effect," says David L. Olive, professor of obstetrics and gynecology at the Yale University School of Medicine. He adds that the aromatase link "is a start, but what we need now is to prove a cause-and-effect relationship for the disease." —*M.S.*

The Ethics of Assisted Reproduction

Medicine can do a lot to help people become parents. Sometimes, maybe too much

by Tim Beardsley, *staff writer*

When Louise Brown, the first baby conceived through in vitro fertilization (IVF), was born in England 20 years ago, commentators fretted that the technique would allow humans to "play God." Tens of thousands of healthy babies later, society has accepted IVF as a treatment for infertility, at least for heterosexual couples. The extensions of IVF that are now being developed, however, give rise to ethical and legal quandaries that are far more challenging than those that surrounded Baby Brown.

Unlike the U.K. and some other countries, which have regulated assisted reproduction, the U.S. has left the field to develop as it will. That development is proceeding at an eye-popping rate: hundreds of millions of dollars are now spent every year on in vitro fertilization. Technological possibilities seem to have run ahead of society's willingness to grapple with the issues they present.

Fertility clinics could, for example, now legally produce babies from biological parents who are both dead, by buying and thawing frozen sperm and eggs that donors banked while still alive. The clinics would combine the components and then implant the resulting embryo in a surrogate mother. There is "no clear technical or legal obstacle to prevent it," says Eric T. Juengst, a bioethicist at Case Western Reserve University. Twins were born last year in Atlanta from frozen eggs that were fertilized after thawing, the first such births in the U.S.

The breakthrough means that "now you can begin to use cadavers" as sources of eggs, says ethicist Arthur Caplan of the University of Pennsylvania. It could happen: "Americans hate people telling them how to make babies," Caplan observes. Last year physicians in California established a pregnancy with an embryo frozen and banked by a woman who had died of cancer. The surrogate mother miscarried.

Already, thousands of babies have been born from frozen embryos. And because scientists can split early-stage animal embryos to create identical twins, they might soon be able to create identical human twin embryos. One could then be implanted and the other stored for implantation years later.

Commerce in genetic materials prompts its own tricky questions, such as whether reproduction is becoming, like plastic surgery, a privilege of wealth. Eggs and sperm are routinely bought and sold through fertility clinics: would-be parents select the gametes on the basis of the physical or mental characteristics of the originators. Thus, embryos themselves "are nearly sold," Juengst says. In a notorious case at the University of California at Irvine's now defunct fertility clinic, scores of embryos were effectively stolen—implanted by clinic staff into would-be mothers without the permission of the donors.

Piecemeal Regulation

Individual states have passed laws to ensure that commercial reproductive services meet quality-control requirements and have put limits on surrogate-motherhood contracts, says Lori B. Andrews of Chicago-Kent College of Law. But the regulation is patchy and does not cover experimental techniques. The U.S. Congress has largely ignored the field because of the political risks of getting near the abortion debate. Controversy swirls even now around the practice of "selective abortion": implanting multiple embryos into a woman's uterus and then surgically eliminating some should too many start to grow.

Americans' strong belief in the right of individuals to reproduce suggests that legal controls on the new techniques "are not going to happen," states Lawrence O. Gostin, legal editor of the *Journal of the American Medical Association*. And some legal theorists believe that that is as it should be. John A. Robertson of the University of Texas, notably, has argued that people who want to be parents have a constitutionally protected right to do so. Robertson points out that few legal constraints limit fertile heterosexual couples who want a baby. So people who need medical help should be subject to no additional legal tests, according to this libertarian view.

Bernard M. Dickens of the University of Toronto says that attitudes toward reproductive technology depend on the opening premise. Some people believe that it should be regulated essentially because it is unnatural. But those who don't agree "must show some harm if they want to restrict reproductive freedom," Dickens asserts. He observes that common attitudes toward reproduction, strongly influenced by traditional religious teachings, are far from gender-neutral. When former Canadian prime minister Pierre Trudeau fathered a child at 71, people applauded this evidence of his vigor. But if a 71-year-old woman bore a child, "many would think that was abhorrent," Dickens says.

Some fear, though, that the anything-goes approach could in fact lead to harm. One possibility is physical harm to the child. Pierre Roubertoux of the National Center for Scientific Research (CNRS) in Orléans, France, has recently repeated his earlier finding that elderly mice that originated as frozen embryos show subtle differences in weight, jaw structure and behavior. Sung-Eun Park and his colleagues at the CHA General Hospital in Seoul have published a report indicating that frozen and thawed human eggs have elevated numbers of chromosomal and other cellular abnormalities.

In principle, such changes could cause problems that might appear only during later life. Joe B. Massey, director of Reproductive Biology Associates, which produced the twins born in Atlanta from frozen eggs, says Park's finding has prompted him to reconsider the technique.

One new procedure for treating male-factor infertility—intracytoplasmic sperm injection (ICSI)—brings with it the possibility of transmitting to offspring a genetic condition that would otherwise not propagate itself. Zev Rosenwaks of New York Hospital–Cornell Medical Center and his colleagues recently used the technique to give men who have the extreme, "nonmosaic" form of Klinefelter's syndrome their own children. Males with this condition have an extra X chromosome in all their cells. They produce very few sperm, but by intro-

ducing individual sperm directly into eggs using ICSI, Rosenwaks has produced healthy babies. Yet male offspring produced this way could be at significant risk of Klinefelter's.

Some doubters of Robertson's libertarian approach suggest governments should enact laws dictating who might be suitable parents, perhaps modeled on the rules governing adoptive parents. Such regulations might avoid tragedies like one that happened in Pennsylvania, in which a 26-year-old bank analyst paid a clinic $30,000 to create an embryo from his sperm and have it carried to term by a surrogate mother. Then, a month after bringing the baby home, he beat the infant to death and pled guilty to murder in 1995. On the other hand, "Would the public sit still for requiring women who wanted IVF to meet adoption criteria?" asks Kenneth Ryan, chair of the ethics committee of the American Society for Reproductive Medicine.

Then there is possible harm to the prospective parents. "My concern is to avoid fraudulent contracts," Juengst states. People who approach a fertility clinic may be especially vulnerable, he believes. A number of the techniques being offered are still experimental, partly because federal funds cannot be used to support research on human embryos. Although professional guidelines attempt to control how clinics advertise their success rates, statistics are irrelevant to a new procedure. So an unscrupulous operator could bilk a fortune out of a would-be parent by offering endless approaches.

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A human egg is held and injected with a sperm (through needle, left) *in intracytoplasmic sperm injection (ICSI).*

Not the least of the possible ill effects from reproductive technology flows from the abstract idea that children have a right to an "open future." If one of two identical twins were to be born many years after the other, the parents who reared the second child would know what kind of talents he or she might develop and so might not allow her to acquire her own wide range of experiences. And when genetic manipulation of human embryos becomes feasible—probably some years from now—parents may want to engineer their offspring so that they can become great dancers or great thinkers.

Fear of Cloning

The question of restricting a child's future could become a pressing issue if researchers ever clone a human. "A cloned child will be a child who is likely to be exposed to limited experiences and limited opportunities," Andrews charges, because the person who produces one will most likely encourage specific characteristics in the child.

In cloning, which made headlines in 1997 with the creation of Dolly the sheep, a nucleus would be taken from a cell donated by the individual to be cloned. The nucleus, containing a complete set of chromosomes, would then be transferred into an egg cell whose own nucleus had been removed. The resulting artificial embryo, implanted into a surrogate mother, would develop into a clone of the original cell donor.

Three bills have been proposed in Congress to ban human cloning, and two are still in play—although no responsible scientist will attempt the procedure anytime soon. Evidence from research on animals suggests that it could give rise to birth defects: during the experiments that produced Dolly, several cloned embryos that miscarried were found to have abnormalities.

Regulation of cloning could be problematic, however. Dickens believes the two bills now in Congress are unconstitutional, and scientists are fighting them because they would prevent important health research. Some emerging techniques related to cloning might, for example, one day be used to grow replacement nerve or skin tissue for transplants.

Another promising technique closely related to cloning has been proposed to allow a woman to have healthy offspring even if she suffers from a heritable disease transmitted in her mitochondria. These are subcellular structures outside the cell nucleus that, like chromosomes, contain genetic material. Andrea L. Bonnicksen of Northern Illinois University notes that in the as yet untested procedure known as in vitro ovum nuclear transplantation, a cell nucleus from a would-be parent with mitochondrially transmitted disease would be transferred into a donated healthy egg cell whose own nucleus had been removed. The hybrid egg would lack the disease-causing mitochondria of the parent.

The regulatory mess might be clarified soon. The American Bar Association has formed a committee to draft a "model act" that states could use as a basis for their own legislation. According to H. Joseph Gitlin, its chair, the act should protect the rights of children conceived through IVF and establish the legal status of genetic materials. It should also provide consumer protection for prospective parents.

The Food and Drug Administration and the Centers for Disease Control and Prevention are now considering regulating the fertility business. But the proliferating ways of bringing children into the world will continue to challenge society's tenuous ethical consensus. The conundrums are profound.

While desperate prospective parents undergo risky procedures to have a shot at acquiring children genetically related to themselves, thousands of unwanted youngsters wait in vain to be adopted. Yet "it seems that all that we prize about the parent-child relationship is present with adopted children," Dickens notes.

And while ethicists debate new reproductive technologies, 600,000 women worldwide die each year from complications linked to pregnancies initiated in the traditional manner, says Rebecca J. Cook of the University of Toronto. The overwhelming majority could be saved with properly trained birth attendants and inexpensive medicines. But most of these deaths are in developing countries, and the developed world applies quite different ethical standards to faraway lands. SA

Get Moving

Researchers debate how much exercise is enough

by Stephanie J. Arthur, *staff writer*

J. W. STEWART

Ever find yourself making that resolution to get into shape and then an hour later trading in that trip to the gym for the more appealing prospect of curling up on the sofa with a good book or the remote control? You're not alone. Despite decades of encouragement to exercise for health, 60 percent of Americans are not regularly active, and 25 percent are not active at all, according to a 1996 report from the U.S. surgeon general. In today's fast-paced world, many people feel they don't have enough time to exercise, particularly when it's hard to figure out how much exercise is really enough.

One of the major prescriptions for how much people should be exercising was developed in the mid-1970s by the American College of Sports Medicine (ACSM). The ACSM proposed that 20 to 30 minutes of continuous, vigorous activity, such as running—keeping your heart rate at 60 to 80 percent of its maximal level—at least three days a week would help individuals garner substantial health benefits. (To calculate your maximal heart rate, use the formula 200 – age = maximum beats per minute.) Most people, however, found the intense level of activity too strenuous or the amount of time too difficult to fit into their busy schedules, so the guideline had little influence.

To amend this problem, the Centers for Disease Control and Prevention (CDC) teamed up with the ACSM to create a recommendation that would be less intimidating but would still promote health and fitness. The guideline, published in 1995, recommends a total of 30 minutes of moderate exercise—for instance, brisk walking at 40 to 60 percent of your maximal heart rate, rather than running—at least five days of the week. One important aspect of the new guideline is the concept that you can accumulate exercise points throughout the day, working out for short periods—three 10-minute sessions, for example—as long as the combined time is at least 30 minutes.

JoAnn E. Manson of Harvard Medical School has studied the effects of exercise on women and explains the advantages of such activity: "There is good evidence that even moderate-intensity exercise—such as brisk walking—will lower your blood pressure, improve your lipid profile by increasing the levels of protective HDL [high-density lipoprotein, the good cholesterol], improve insulin sensitivity, lower blood sugar levels, lower risk of cardiovascular disease and osteoporosis, and it may also have benefits in terms of reducing stress."

Russell R. Pate of the University of South Carolina, a co-author of the CDC-ACSM report, says that although he and his colleagues did ease the exercise burden, "it's [still] a reasonable amount of activity—and a good deal more than most adults in this country are getting already." Pate emphasizes that "what we need to communicate is that there's more than one way to skin a cat here." The report merely spells out the minimum requirement for beneficial physical activity. Neophyte exercisers don't have to run marathons to be fit, but marathon runners needn't cut back to brisk walking, either.

The value of accumulated exercise is controversial among researchers. Manson, who advises her patients to exercise "at least 30 minutes per day and no less than 15 minutes per session," believes that accumulated activity is likely enough to burn calories and thus lead to weight loss but that sustained exercise is necessary to benefit the heart and lungs.

Pate takes a slightly different approach, asserting that current studies show that smaller "packages" of activity do provide cardiovascular advantages. This approach may be beneficial in other ways as well. For example, the body's metabolism remains high for some time after exercising, so by repeatedly working out, even for short periods, you reap the physiological rewards, such as burning calories, more often throughout the day.

Pate looks at the issue from an evolutionary standpoint. "Our predecessors didn't run intervals or jog for half an hour. What they did was follow animals around; they were hunters and gatherers, and that's the way our bodies evolved. And what is hunting and gathering? It's accumulating moderate-intensity physical activity throughout the day." Some researchers disagree with this analysis, but until more conclusive studies come forth, Pate urges people "to at least stay open-minded."

As a strong proponent of sustained exercise, Paul T. Williams of Lawrence Berkeley National Laboratory argues that the advantage of accumulated exercise is "currently an unproved hypothesis." Williams's studies on female runners have revealed that health benefits increased the longer the women exercised. For instance, the women who ran 64 kilometers (40 miles) per week had on average 10 percent higher concentrations of HDL than women who ran 24 kilometers (15 miles). One important implication of this study: even if you're already active and in good physical condition, more exercise can be good for you.

But Manson fears that Williams's doctrine of extended exercise is "not realistic or necessarily safe" for all women. She concedes that Williams's data are valid, but she also worries about certain health risks—such as recurring musculoskeletal injuries, cessation of menstrual cycles and even infertility caused by altered levels of estrogen—that are more likely to occur as women increase the length and vigor of their exercise sessions.

Debates aside, experts do agree that a sedentary lifestyle is tremendously unhealthy, often leading to a variety of chronic diseases and even premature death. Studies have shown that exercise lowers your risk for heart disease; Manson adds that "there's also strong evidence that it may lower risk of certain cancers, particularly breast and colorectal cancers, which are the second and third leading causes of cancer death for women."

So will the new CDC-ACSM recommendation finally get more people moving? Pate comments that it's too soon to tell, but he and his colleagues will be watching closely over the next several years. As the value of exercise becomes only more and more apparent with each new study, it's no wonder experts keep encouraging people to be more active. After all, done wisely, exercise is, as Manson says, a "win-win situation." SA

LENNART NILSSON From *Behold Man*

Searching for Preeclampsia's Cause

Researchers zero in on one of the most dangerous disorders of pregnancy

by Kathryn Sergeant Brown, *special correspondent*

Michelle Wemple had a picture-perfect pregnancy. She hiked. She ate well. She felt healthy and hopeful. So her 36th-week prenatal checkup came as a shock. For some reason, Wemple's blood pressure was soaring. A urine test also showed her kidneys were leaking protein. Her doctor suggested inducing labor—immediately. "How could things suddenly go so wrong?" Wemple asked. "I'd done everything I possibly could to be healthy. And I didn't feel sick." Yet Wemple—like one in 20 pregnant women—had preeclampsia.

Women with preeclampsia, which is also called toxemia of pregnancy, suddenly develop high blood pressure and begin to retain fluid and excrete vital proteins. If the baby isn't delivered quickly or the physician can't lower the woman's blood pressure using drugs, the condition can progress to full-blown eclampsia, which brings on deadly seizures.

Doctors do not know why some women develop preeclampsia—or how to respond, short of administering blood pressure drugs and delivering the baby as soon as possible, sometimes too early for it to live. But that could soon change. More than a dozen labs worldwide are now studying preeclampsia. Their findings could help doctors rate every pregnant woman's risk of the disorder. And although a specific therapy is still years away, researchers hope they might one day have more to offer women with preeclampsia than just a rushed delivery. "Our understanding of preeclampsia is quickly improving," says James M. Roberts, director of the Magee-Womens Research Institute in Pittsburgh. "We've moved further in the last few years than we have in the past 50."

During a normal pregnancy, mother and baby quickly form a tight biological bond. Early on, fetal cells form the placenta, a lifeline that ferries nutrients and oxygen from the mother's uterus down the umbilical cord to the baby. Some pioneer placental cells actually enter uterine blood vessels, elbow out the maternal cells lining the vessels and then stretch the vessels, enabling them to shuttle more blood as the fetus grows.

A four-month-old fetus is seen cocooned in the amniotic sac.

But in preeclampsia, scientists say, this cooperation falters. According to one scenario, too few placental cells enter uterine blood vessels—and those that do simply lie around, rather than flattening out and expanding the vessels. Alternatively, a mother's blood vessels might be stiff and resist expansion because of prior hypertension or diabetes. "Preeclampsia can come from either the fetal or maternal side," says Kenneth Ward of the University of Utah.

In either case, the result is a poorly developed placenta that spells trouble for both mother and child. The baby gets meager rations of oxygen and nutrients, and the mother's body senses damage to uterine blood vessels and reacts in a variety of ways. Her small arteries spasm, boosting blood pressure. Her blood vessels may leak water, causing rapid weight gain and swelling. Her level of platelets, specialized cells that clot blood, can plummet. Last, her kidneys may begin to fail, expelling vital proteins along with the usual metabolic waste.

Most women with preeclampsia develop a mild case late in pregnancy, when their baby can be delivered safely, as Wemple's ultimately was. But if a woman falls ill before the third trimester, her premature baby might not survive.

Deciding who is at risk for preeclampsia is tricky. The condition tends to run in families and to affect first-time mothers. Existing hypertension, diabetes or kidney disease raises a woman's susceptibility. Beyond these broad parameters, however, doctors are unable to predict which women will become sick. To define risk better, scientists are hunting for biochemical flags that warn of the possibility of preeclampsia.

Ward and his colleagues reported that women who inherit a variant of a gene encoding a common blood-clotting protein called factor V tend to form blood clots in their placentas, which could lead to preeclampsia. The researchers also found high rates of preeclampsia among women with an abnormal version of angiotensinogen, a protein that helps to control blood volume throughout the body and signals uterine blood vessels to expand during pregnancy. They are now analyzing the angiotensinogen-preeclampsia link among 24,000 women. If the connection pans out, it might yield a blood test to identify women at risk as early as their first prenatal checkup.

The placental cells themselves could also offer tools for predicting which pregnant women might be prone to preeclampsia. For example, Susan J. Fisher, Yan Zhou and their colleagues at the University of California at San Francisco are now analyzing the repertoire of proteins made by cells isolated from the placentas of women who had preeclampsia. Any placental proteins that occur in unusual amounts during preeclampsia might become diagnostic markers; however, a blood test based on such a protein would be years away.

Yet without a treatment or preventive for preeclampsia, knowing one's risk is only half the battle. A surefire preventive has been elusive. A handful of studies linked low-calcium diets to high preeclampsia rates in Latin America, suggesting that calcium supplements might prevent the disorder. But last year, a major study conducted by the National Institutes of Health found that calcium does not prevent preeclampsia in otherwise healthy women. Hopes also rose—and then fell—over aspirin, which is thought to relax blood vessels, thereby lowering blood pressure. Some scientists now suggest that antioxidants might prevent preeclampsia. But Richard J. Levine of the NIH, who headed the calcium study, is skeptical. "We need to know a lot more about this disease before we can block it," he says.

In fact, doctors might never cure a single disease called preeclampsia—because, like heart disease or cancer, the disorder could come in several varieties, supposes John T. Repke, chairman of obstetrics and gynecology at the University of Nebraska Medical Center. Just as breast and lung cancers are treated differently, preeclampsia caused by fetal cells or a mother's rigid blood vessels—or something as yet undiscovered—might warrant unique therapies. According to Repke, pinning down preeclampsia's cause in just a subset of women might prove easier than solving the entire puzzle. In the meantime, the best thing a woman can do is stick with prenatal checkups. SA

What Determines the Timing of Birth?

Why newborns arrive on their own schedule—not yours

by Kathryn Sergeant Brown, *special correspondent*

Babies arrive unannounced. Some show up three weeks early. Others appear 10 days past term. Their timing seems random—but it's not. Together the fetus and placenta establish the moment of childbirth by launching a chemical cascade that sets off a mother's contractions. The question is, How does this embryonic duo set the date?

Scientists are now pursuing two main scenarios. According to the first, the placenta runs on a nine-month clock, telling time by the flux of pregnancy hormones. Your clock may run fast, causing an early birth, or slow, bringing a late baby. According to the second, the fetal brain acts like a computer, logging its own growth or the environmental changes until the moment for birth is right. Exploring both ideas, researchers have found telltale hormonal changes that portend premature birth. By picking up on and manipulating these hormonal cues, doctors could one day prevent some babies from being born before their time.

One in 10 babies is born prematurely, which is defined as before the 37th week of pregnancy. Not yet fully developed, these tiny newborns can succumb to serious respiratory infections or to neurological problems such as cerebral palsy. Preterm birth is the leading cause of infant death in the U.S. What is more, because there is no reliable way to tell which women are likely to deliver prematurely, all doctors can do is closely watch women who have risk factors for early delivery. Such risk factors include having had a premature baby previously, abusing drugs or alcohol, smoking or harboring an untreated vaginal infection.

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But some researchers suggest that—in humans, at least—this hormonal relay begins in the placenta, not in the baby's brain. The placenta thrives for nine months, after which its cells rapidly die off. Somehow, scientists reason, the placenta must be keeping time. "[Birth timing] is probably much like the onset of puberty and menopause," says Roger Smith of the University of Newcastle in Australia. "These are major biological events that are preprogrammed to occur at certain points." Smith suggests that heredity might determine whether a woman has a fast- or slow-running birth clock or one that runs on time. Preterm births sometimes run in families, he says.

How does the placental clock tell time? Possibly by following the flux of pregnancy hormones. One example is corticotropin-releasing hormone (CRH) produced by the placenta. CRH rises and falls in a woman's blood throughout pregnancy, peaking in the weeks before birth, when it causes estrogen to increase as well. Every pregnant woman appears to have a unique CRH pattern during pregnancy, suggesting a personal timetable.

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If Smith's study is confirmed, doctors might one day check a pregnant woman's CRH level to learn whether she's likely to deliver prematurely. If her CRH levels are high, the physician might prescribe drugs to prolong pregnancy or prenatal corticosteroids to speed a fetus's lung development. In the future, Smith says, drugs specifically intended to lower CRH could possibly delay delivery as well.

In addition to CRH, estriol—a form of estrogen—also might be part of the placental clock. Biex, a biotechnology company in Dublin, Calif., is now developing an estriol-based test for premature delivery. Three weeks before childbirth, estriol levels in a pregnant woman's blood peak, explains James A. McGregor of the University of Colorado at Denver. He has worked with Biex to develop SalEst, a test that detects this estriol crest in a woman's saliva, which mirrors levels in the blood.

In clinical studies, SalEst—which has received preliminary Food and Drug Administration approval—correctly predicted 57 percent of preterm births. Women with known risk factors could take the test several times near the end of their pregnancies to see if they really were likely to deliver prematurely.

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Putting a slight spin on the fetal-computer concept, Caroline McMillen of the University of Adelaide in Australia suggests that birth begins when a fetus's brain senses a drop in oxygen and glucose in the womb. Near the end of pregnancy, as the fetus grows, the nutrients it receives from the placenta become inadequate, McMillen says. The result, in short, is stress.

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A decade ago that wish list could not be fulfilled. Anything that gave the mother some relief, it seemed, threatened the baby or slowed labor, increasing the chances of a cesarean section. For instance, narcotics, such as a shot of Demerol, would ease a mother's pain but could interfere with the baby's breathing. Similarly, spinals and epidurals—in which physicians inject painkillers into the sac surrounding the spinal cord or into the epidural space just outside it—would numb the spinal nerves that transmit the pain of uterine contractions but could also make it hard to push. Indeed, women would often be too weak to get out of bed during labor. And spinals could also leave the mother with a ferocious headache caused by the leakage of spinal fluid from the needle puncture.

Although some women eschewed painkillers during labor because they wanted to experience natural childbirth, others wanted relief. But given the risks, many women felt obligated to forgo medication. Some women also succumbed to guilt: during the 1960s, 1970s and 1980s, the social pressure for natural childbirth became so intense that in some quarters there was a sense of shame or dishonor attached to asking for pain medication during labor.

Times have changed. "What anesthesiologists can now provide for pain relief is a lot closer to a natural delivery than it was 10 or 12 years ago," says Richard M. Smiley, director of obstetric anesthesiology at Columbia-Presbyterian Medical Center. "In the vast majority of cases, we're able to achieve 95 to 100 percent pain relief, and the woman is still relatively mobile and still has complete strength."

The trick lies not in a revolutionary new therapy but in combining familiar drugs in new ways for spinal and epidural anesthesia. In the past, doctors giving epidurals would inject a Novocain-like local anesthetic into the epidural space in a woman's spine and leave in the catheter so that additional medication could be injected later. The drug would numb everything below the waist but would also cause considerable weakness. "It was difficult to push," Smiley says, and the medication could sometimes interfere with contractions and impede labor.

Today doctors add small amounts of opioid drugs such as fentanyl to the epidural injection. Opioids ease pain without causing weakness and allow the dose of the Novocain-like drug to be reduced by up to 75 percent. Women remain strong and able to push, and Smiley says he has seen no convincing evidence that this type of anesthesia interferes with labor, although there is still some debate about whether it does.

With the new epidural technique, women may still feel some discomfort and pressure, Smiley notes, but little pain. The technique is most effective during the first stage of labor, which is considered the most painful. The uterine contractions and dilation of the cervix that occur during the first stage produce a visceral type of pain that is particularly hard to tolerate. Most women find it easier to endure the pain of the second stage of labor, in which they deliver the baby through the birth canal.

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Q&A

The Genetics of Breast and Ovarian Cancer

MARY LEVIN *University of Washington*

Mary-Claire King, Ph.D.

What if you could gaze into a crystal ball and learn that breast or ovarian cancer lies in your future? It's a frightening possibility—and one women who come from families with the cancers now face. Today's crystal ball is a high-tech blood test. Analyzed in a lab, the DNA in your white blood cells can reveal mutations in two genes, BRCA1 *and* BRCA2, *that put you at great risk for familial breast or ovarian cancer. And that's the easy part. It's then up to you to make tough health decisions—whether getting frequent mammograms and ultrasound exams of your ovaries or opting for radical surgery to remove your breasts or ovaries.*

Scientists discovered BRCA1 *in 1994 and* BRCA2 *a year later. Now they are unraveling how the genes work—and why they sometimes don't. One researcher at the forefront is* **MARY-CLAIRE KING, Ph.D.,** *a molecular geneticist at the University of Washington. King has analyzed mutations in* BRCA1 *and* BRCA2 *in hundreds of families. She speaks with* **KATHRYN SERGEANT BROWN,** *special correspondent for* SCIENTIFIC AMERICAN, *about the genetics of breast and ovarian cancer. One of King's most important messages is that most breast cancers are not caused by inherited mutations.*

Q ***To understand inherited breast or ovarian cancer, it's important to know how the responsible genes,* BRCA1 *and* BRCA2, *normally work. What do these genes do in the body—and what goes wrong to cause cancer?***

A We don't know, in full, what the genes do. We do know that *BRCA1* and *BRCA2* control the proliferation of breast epithelial cells—that is, the cells that line the milk ducts in the breasts—and ovarian epithelial cells, the cells on the surface of the ovaries. Some scientists have suggested we call *BRCA1* the "cruise control" gene for breast and ovarian cells because it works to keep cells growing and dividing at the right pace. Without normal versions of *BRCA1* or *BRCA2*, breast or ovarian cells can multiply out of control. That's the ultimate consequence. But the mechanism isn't fully understood. Scientists have found hundreds of inherited mutations in *BRCA1* and *BRCA2* that can lead to cancer, and new mutations are found every day.

If a woman inherits a faulty version of* BRCA1 *or BRCA2, how likely is she to get breast or ovarian cancer?

In the U.S. population as a whole, a woman has a 10 percent chance of developing breast cancer by the age of 85. That risk increases to more than 80 percent among women with inherited *BRCA1* or *BRCA2* mutations. In general, fewer than one in 100 women develop ovarian cancer. Women with inherited *BRCA1* or *BRCA2* mutations have at least a 40 percent higher risk for ovarian cancer.

Who's at Risk

When it comes to cancer, genetics is only part of the story. For instance, researchers blame* BRCA1 *and* BRCA2 *for only 5 percent of the 180,000 breast cancer cases that occur every year in the U.S. What explains the rest?

We know two clear classes of environmental factors play a role in breast cancer. One is exposure to radiation as a young woman. It's a rare event, but it has a dramatic impact on risk. For example, girls surviving the atomic bomb blasts at Hiroshima and Nagasaki subsequently had four times the rate of breast cancer as other Japanese women their age.

The second class of risk factors is related to estrogen. The earlier a woman begins to menstruate and the later she has her first pregnancy, the higher her subsequent risk of breast cancer. And the later her menopause, the higher her postmenopausal risk of breast cancer. In other words, the longer the interval between puberty and childbearing—during which the body makes estrogens—the higher the risk. Estrogen-rich tissue provides a very healthy milieu for breast epithelial cells to divide, including those with mutations. Of course, most of these mutations will be somatic—that is, not inherited.

Early menstruation and delayed childbearing are probably primarily responsible for the increase in breast cancer rates over the past 50 or 60 years. On average, women today begin menstruating at about age 11. Three generations ago the average age of first menstruation in industrial countries was a few years older. The difference is probably attributable to changes in diet. A well-nourished young girl begins to menstruate earlier, when she reaches a critical weight for height.

Also, many women today have their first child in their early or mid-30s, whereas years ago women began childbearing far younger. Breast cancer occurs very rarely in cultures in which women still begin to menstruate late and have their children at a younger age. Unfortunately, the increased risk of breast cancer in modern women is very much a consequence of being a modern woman. There's no single behavioral or environmental assault that, if it vanished, would drastically reduce the incidence of breast cancer.

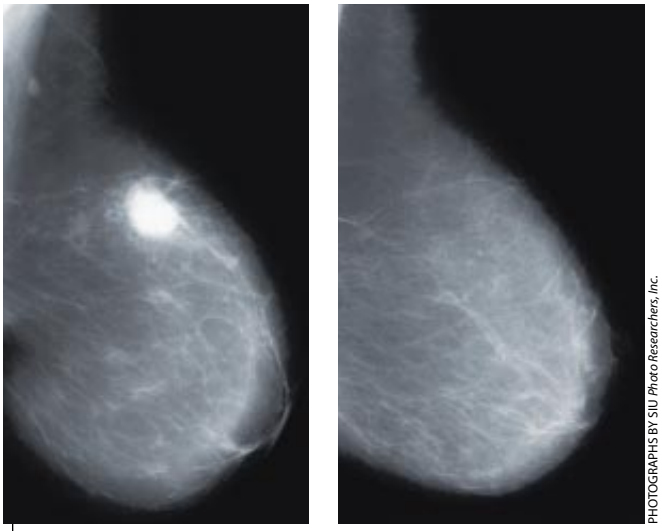
In summary, it's important to note that the vast majority of cancer cases, including breast and ovarian cancer, have nothing to do with inherited predisposition. Most cancers are caused by mutations that occur specifically in cells of a critical tissue, like the breast. Radiation is a mutagen: it causes mutations. Estrogens probably don't cause mutations, but they maintain a cellular environment in which cells can grow and flourish, even if they have mutations.

So far* BRCA1 *and* BRCA2 *have dominated research on the genetics of breast and ovarian cancer. Could another* BRCA *gene be out there waiting to be found?

Certainly. Using mathematical models, we can explain most inherited predispositions to breast cancer—and the vast majority of predispositions to ovarian cancer—by mutations in *BRCA1* and *BRCA2*. But there remain families with many cases of breast or ovarian cancers but no mutations in *BRCA1* or *BRCA2*. If another *BRCA* gene is discovered, it—like *BRCA1* and *BRCA2*—will teach us not only about inherited cancer in some families but also about the general biology of breast and ovarian epithelial cells in women.

Jewish women of eastern or central European descent—Ashkenazi Jews—have an unusually high rate of inherited breast or ovarian cancer. Why? What might these families tell us about how* BRCA1 *and* BRCA2 *cause cancer?

In America the proportion of breast cancer patients with inherited mutations in *BRCA1* or *BRCA2* appears to be highest among Jewish women. Until the past few generations, most Jewish communities tended to intermarry. There are ancient mutations in *BRCA1* and *BRCA2* among people of Jewish ancestry. On the basis of work done in Israel, it appears that at least one of those mutations probably dates back at least 2,500 years.



PHOTOGRAPHS BY SIU *Photo Researchers, Inc.*

Set of mammograms shows a tumor in one of a woman's breasts (left). *Her other breast* (right) *is free of disease. Despite the publicity over the breast cancer genes, only 5 percent of all breast cancer cases are linked to inherited mutations.*

Jewish women with inherited mutations in *BRCA1* and *BRCA2* provide unique insight into the causes of breast cancer. With clinical colleagues in New York City, we have been studying breast cancer patients of Jewish ancestry and their families. About 10 percent of breast cancer patients who identify their ancestry as Jewish have one of these ancient mutations in *BRCA1* or *BRCA2*. By tracing the histories of these mutations in the families of these women, we can ask several important questions. Among women with a *BRCA1* or *BRCA2* mutation, what is the actual risk of breast cancer developing by the age of 30, 40 or 50? What's the risk of ovarian cancer developing by those same ages?

By working with these families, we can also learn how the genes interact with the environment. Are there any differences in environmental exposures among women with *BRCA1* or *BRCA2* mutations who developed breast or ovarian cancer compared with those who have not? Are there other differences in life experiences that can be identified? By first evaluating genetics and then asking questions about nongenetic factors, we hope to get a better handle on both.

Getting Tested

Following the discovery of* BRCA1 *and* BRCA2*, companies scrambled to develop blood tests that could detect cancer-causing mutations in the genes. Today a number of commercial firms offer these DNA tests. How should a woman decide whether to take a test for a* BRCA1 *or* BRCA2 *mutation—and what should she do if the results come back positive?

A woman might consider genetic testing if she's from a family with a severe history of breast or ovarian cancer. In a recent publication in the *Journal of the American Medical Association*, we suggested that in the American population generally, families

at high risk of having inherited mutations in *BRCA1* or *BRCA2* are families with both breast and ovarian cancers or at least four cases of breast cancer. Some Jewish women consider genetic testing if the family history is less severe because the frequencies of inherited *BRCA1* and *BRCA2* mutations are higher. Also, screening all of *BRCA1* and *BRCA2* involves testing about 18,000 nucleotides, or units, of DNA. Women from populations with ancient mutations often choose to be screened for more common mutations first. Then they may decide to have complete sequencing undertaken. But one can't exclude the possibility of a mutation without screening all of both genes. It's labor-intensive and expensive.

Let's suppose a woman's mother developed breast cancer and has an inherited mutation in *BRCA1* or *BRCA2*. This woman has a 50–50 chance of inheriting a mutation. If she does inherit the mutation, her risk of breast and ovarian cancer is much higher than that of other women, but it's not 100 percent. One of the greatest frustrations in this work is the level of uncertainty that remains about the biology.

If a woman learns she has an inherited mutation in *BRCA1* or *BRCA2,* what are her choices? At present, interventions are close to the extreme. On one hand, she can be screened carefully by mammogram and physical exam for breast cancer—and possibly by ultrasound for ovarian cancer. At the other extreme, she could have prophylactic surgery to remove her breasts (mastectomy) and/or ovaries (oophorectomy). It's very frustrating not to have less drastic but proactive interventions available yet.

Are mastectomy and oophorectomy foolproof ways to stay cancer-free?

Surgeons point out that the removal of the breast does not always remove all cells vulnerable to the development of cancer. Biologically, there is legitimate concern that one hasn't removed the risk completely. Current studies from the Mayo Clinic, however, suggest that prophylactic mastectomy greatly reduces the subsequent risk of breast cancer for women.

One drawback to genetic testing is that a person may later experience discrimination at work or when applying for health insurance. Lawmakers have proposed several bills to prevent health insurers from restricting coverage based on genetic tests. Has genetic discrimination been a big concern to you?

Yes. One thing that makes genetic testing difficult is that it's all bound up in an insurance industry that, until recently, has been able to penalize people on the basis of their genotype. The reality is that all of us carry genes that predispose us to something. We just happen to have identified those genes for breast and ovarian cancer.

It's essential that a woman be able to take advantage of technology to make decisions about health care without worrying that she's preventing her access to that very care. It's life-threatening to be unable to get adequate health care. That's why the legislation to separate the availability of health care from genotype is absolutely critical. I hope that new laws will make this debate moot in the next few months.

In the future, what choices might women have in testing for or treating inherited breast and ovarian cancer?

Two approaches are under investigation. One is very early diagnosis—that is, detection of breast tumors when they're less likely to be invasive, using the combined techniques of molecular biology and screening through mammography and breast exams. Another area is chemoprevention. For example, the tamoxifen prevention trial just indicated that taking the drug tamoxifen, which blocks the estrogen receptors in breast cells, reduces breast cancer risk. Now we need to see whether it works in women with inherited mutations in *BRCA1* or *BRCA2*.

In the next several years, we hope to sort out the biology of familial breast cancer well enough to offer women with *BRCA1* or *BRCA2* mutations a series of intermediate choices between mammography or ultrasound screening and surgery. SA

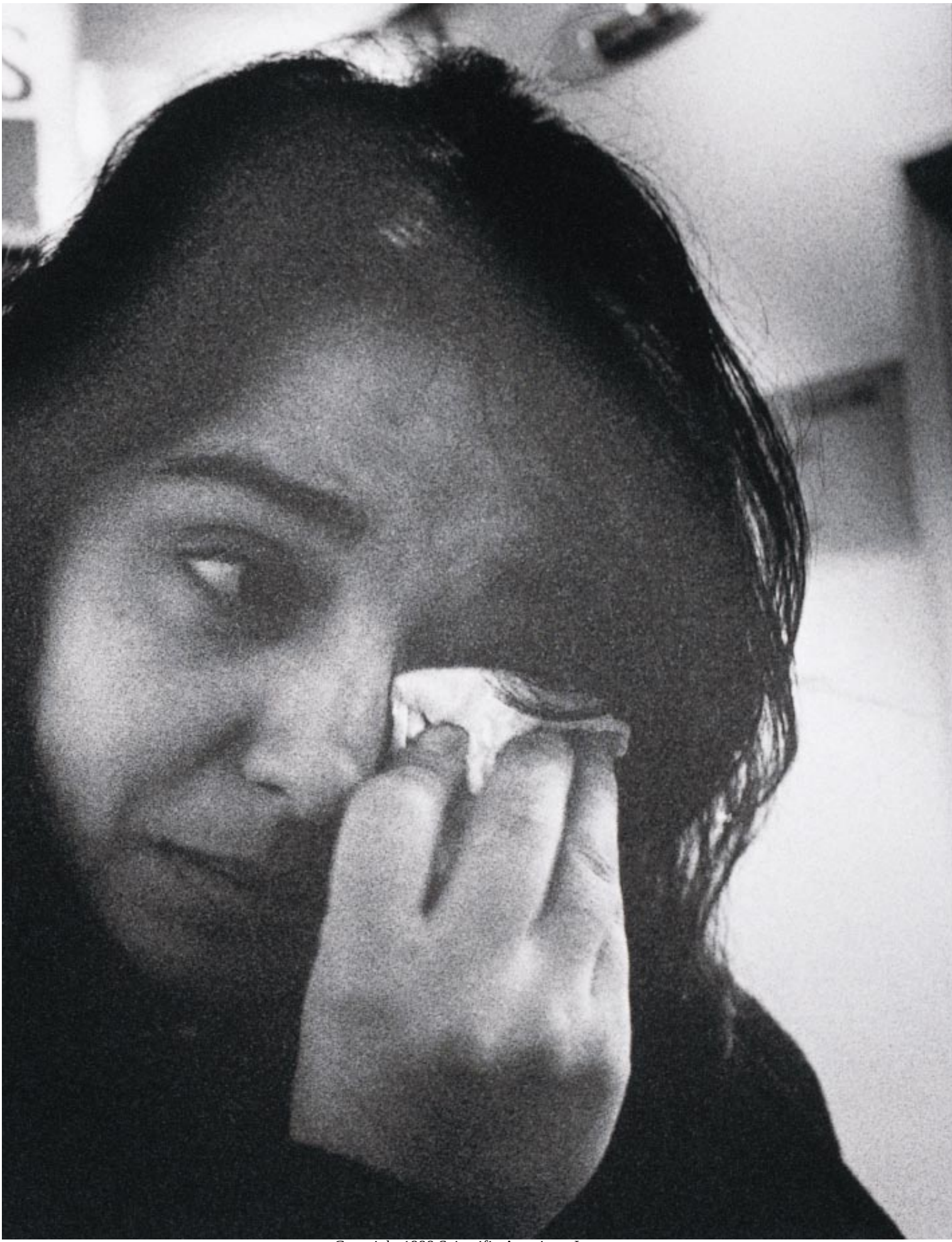
BRCA Testing Basics

Two companies offer genetic testing for *BRCA1* and *BRCA2* mutations in the U.S.:

Company: Myriad Genetics
Test name: BRACAnalysis
Test types: Full *BRCA1* and *BRCA2* gene analysis for breast and ovarian cancer susceptibility; three-mutation analysis for Ashkenazi Jewish women; single search for known family mutations
Cost: $395–$2,400
Results: Within four weeks
How to get tested: Ask your doctor to order Myriad's test kit and information packet
For more information: 800-469-7423; http://www.myriad.com

Company: OncorMed
Test names: Stage I, Stage II, Stage III, Heritage Panel
Test types: Screening for 98 percent of known *BRCA1* and *BRCA2* mutations, from most to least common: Stage I screens for the top 40 percent of *BRCA1* mutations and 27 percent of *BRCA2* mutations; Stage II, the next 40 and 37 percent, respectively; Stage III, the next 18 and 34 percent; Heritage Panel test screens for three known mutations in Ashkenazi Jewish women
Cost: $300–$800 per test
Results: Within three, four or 10 weeks, depending on the test
How to get tested: Ask your doctor to order OncorMed's test kit and information packet
For more information: 800-662-6763; http://www.oncormed.com

For more information, contact the National Alliance of Breast Cancer Organizations at http://www.nabco.org on the World Wide Web or call 800-719-9154. The National Cancer Institute also has information on breast and ovarian cancer; contact the institute at http://rex.nci.nih.gov or call 800-422-6237.



The Consequences of Violence against Women

Violence is a vicious cycle that harms women and their families

by Lisa A. Mellman, M.D.
Columbia University

Society is riddled with violence. In 1995 some eight million people were assaulted in the U.S. Homicide was the second leading cause of death among 15- to 24-year-olds and the principal cause of death for 15- to 24-year-old black men. Of the several thousand women murdered each year (4,654 in 1995, according to the Department of Justice), one quarter to one half are killed by their male partners—and many were battered by these men in previous incidents. The homicide rates for children and adolescents have doubled since the early 1960s, and teenage girls are at least 13 times more likely to have been raped or sexually assaulted than teenage boys. The impact of this violence is pervasive, with profound physical, psychological, economic and social consequences for everyone.

Because violence against women largely takes place at home, it has a particularly insidious character and effect. Women are seven times more likely than men are to experience violence committed by someone close to them, by a lover, spouse or ex-lover. This corruption of trust and intimacy means that primary relationships are disrupted throughout the household and that a vicious cycle is set in motion—one that is at risk of being perpetuated by the next generation.

Violence and neglect beget violence and neglect. All children can become scarred and depressed by abuse that they observe or receive. Although most mistreated children do not become violent adults, one third may become abusive or neglectful parents; one third are at risk of becoming violent. Only by realistically assessing and facing the full scope and consequence of violence against women can health care professionals and political advocates make some headway in combating it. Fortunately, better-designed epidemiological studies are clarifying prevalence and are increasingly documenting the long-term medical and psychological effects of violence on women and their children.

All too often women remain in abusive relationships. This woman was a victim of domestic violence for four years before filing a complaint.

SADIN *Liaison/Rapho*

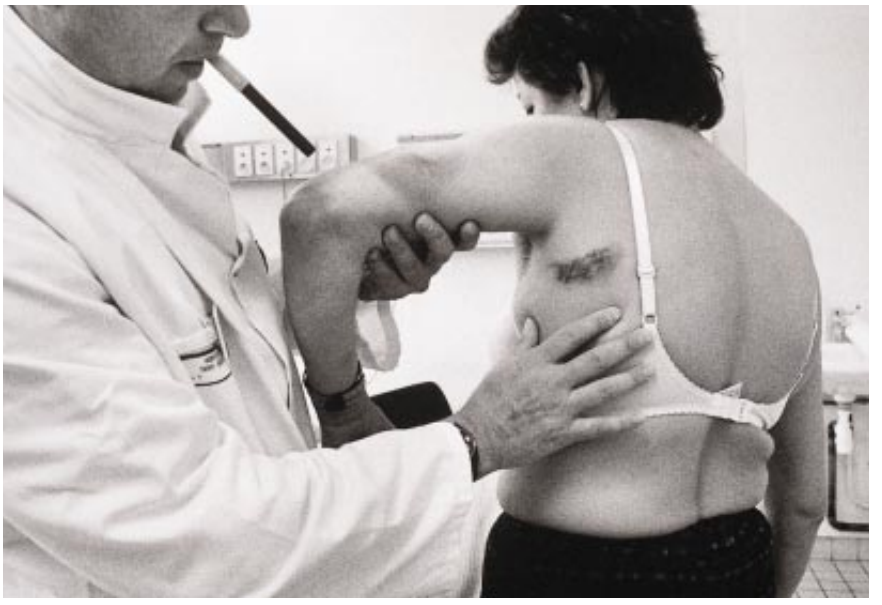
Numbers at Odds

Arguments revolving around statistics have long plagued discussions about how to gauge the prevalence of violence. In part, the problem has arisen from semantics. Survey results differ depending on how exactly terms are defined. For instance, various studies have imprecisely defined terms such as "rape" or "domestic violence." Domestic violence has sometimes been interpreted as being hit repeatedly and other times as being grabbed once in the course of a relationship. The same problem applies to the ambiguous phrases "intimate relationship" and "physical injury." In addition, methodology shapes outcome. Face-to-face interviews, for example, yield higher numbers than do those conducted over the telephone. (The figures given in this article are the best ones available to date, but it is certain that some of them also suffer from these confounding factors.)

Only recently have epidemiologists precisely clarified their terms. Today we know from solid studies that 36 percent of American women—that is, more than 34 million women—report experiencing violent events (including rape and sexual or physical assault) or the homicide of someone they knew well. And between 9 and 12 percent of women report being raped at least once.

The data on violence by intimate partners remain less clear, however. Research using more

Police and doctors are called in for only a small number of cases of domestic violence.



exact methodology and larger samples is under way, including a large study funded by the Centers for Disease Control and Prevention (CDC) and the National Institute of Justice (NIJ). Results from this study will be available later this year. But for now we have to rely on older estimates: every year between 1.8 and four million women are battered by their partners.

Assessing the medical and psychological aftermath of this violence has been difficult to quantify as well, but for reasons other than terminology. Instead the challenge has been establishing causality between a violent event and a later physical or psychiatric symptom. Women often experience more than just violence: familial dysfunction and neglect usually coexist with physical or sexual abuse, or both. This confluence makes it difficult for physicians to tease apart which factors are contributing to an illness. In addition, abused women may develop more than one psychiatric disorder and may show symptoms long after a traumatic event took place.

These complexities are further compounded by the stigma and shame that abused women feel. According to a report by the Commonwealth Fund, 90 percent of women who described themselves as physically abused by their partner or spouse had never told a doctor. Even when directly asked, women often deny being beaten or assaulted. Some feel embarrassed about their situation and frightened of their batterer; others are understandably terrified about addressing the serious problems of their relationship. To confront the batterer means risking his denial or revenge. To leave means facing the daunting task of securing housing and work—efforts often complicated by the need for child care and the lack of economic or emotional self-sufficiency.

A Nightmare of Body...

Although precise numbers remain elusive for the time being, the medical and psychological effects of domestic violence are nonetheless becoming terribly clear. In 1991 the American Medical Association began a campaign to educate physicians—and the country at large—about domestic violence. Studies have documented that victims of violence and their children make more visits to physicians and have more medical complaints than most people do. Indeed, researchers found that the average number of physician visits increased 31 percent for assaulted women and 56 percent for rape victims in the year after the crime against them. Only in the past few years, however, have physicians begun to be trained to recognize and treat abuse.

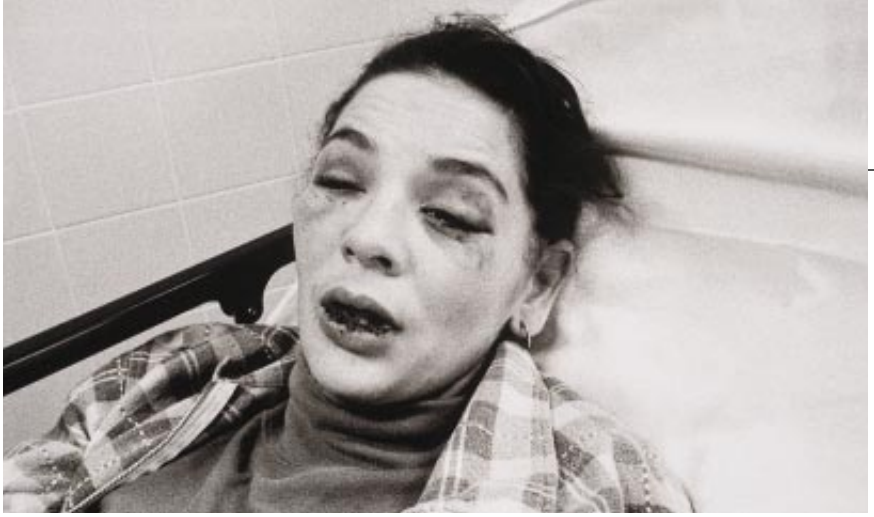
Even a cursory look at the injuries women incur explains why the resulting medical costs for domestic violence in the U.S. have been estimated at between $5 billion and $67 billion annually. Women suffer not only transitory injuries such as bruises, cuts, broken bones, concussions and urinary tract infections but also permanent ones: joint damage, hearing or vision loss, chronic pain, irritable bowel syndrome and sexually transmitted disease, including HIV infection.

Pregnant women are especially at risk of complications related to abuse. Studies indicate battered women have almost twice the number of miscarriages as nonbattered women do. Battered women often start prenatal care late in pregnancy and may have a greater number of low-birthweight babies. Because substance abuse is more prevalent among abused women, their fetuses are more likely to suffer drug- and alcohol-related complications.

...and of Mind

The psychiatric consequences of violence are also proving to be wide-ranging and severe. Survivors often describe a pervasive sense of terror and loss of control during and after the assault. Acute stress disorder (ASD) or posttraumatic stress disorder (PTSD) often follows violent events. Both are characterized by flashbacks and nightmares, numbness and avoidance, and heightened alertness—including irritability, vigilance, overresponsiveness to touch or sound, and an increased capacity for being startled.

Stress disorders are much more prevalent in victims of physical and especially sexual assault than they are in people



PHOTOGRAPHS BY SADIN *Liaison/Rapho*

Domestic violence leaves lasting scars, emotionally and sometimes physically.

who have not experienced such violence. In one survey, more than 94 percent of women who had been raped developed ASD within the first month, and 47 percent of these women had PTSD after three months. Extrapolation from several studies suggests that of the estimated 12 million or so American women who have been raped, almost four to five million have suffered PTSD.

Physiological studies demonstrate that the stress response evoked in PTSD is distinct from the normal stress response—and from the response reported in other psychiatric disorders. Individuals with PTSD have low cortisol levels and greater cortisol fluctuation, which indicates that their stress response has been biologically altered. These chemical changes may translate into a more reactive heart rate and a tendency to startle easily.

Violence and abuse are frequently associated with other disorders as well: depression, anxiety, substance abuse and feelings of being disconnected from reality. Women who were repeatedly raped in childhood are three times more likely to develop depression and almost five times more likely to develop anxiety disorders than women who have not suffered in this way. Abused women also suffer from low self-esteem and poor interpersonal skills and feel inherently bad or dirty. They blame themselves for what has happened. These feelings make them unwilling to take care of themselves—and thus unwilling to seek help or to comply with medical care.

Many women who have been victimized are at higher risk of having chronic sexual problems, mutilating themselves, running away from home as teenagers and entering into prostitution. They are more likely to abuse substances; according to one report, 75 percent of women in substance-abuse treatment programs have a history of sexual abuse. The risk of attempted suicide increases dramatically in women who were sexually assaulted before age 16.

The implications for children are immeasurable. Not only is it damaging to grow up with a primary caretaker who is consistently depressed or suffering from PTSD, but as targets of and witnesses to violence, children are deeply harmed. Basic trust, the first developmental stage in psychoanalyst Erik H. Erikson's lifecycle theory, is completely disrupted. Normal expectations—that parents and caretakers are protectors, that daily life is predictable, that your body is your own—may be permanently crushed. When violence is enacted toward a child, it may disrupt normal development, setting the stage for lifelong difficulty.

At least three million children in the U.S. witness parental abuse annually; between 40 and 70 percent of children entering battered women's shelters are abused, mostly by the mother's abuser but sometimes by the mother herself. Children suffer behaviorally and intellectually from seeing violence in abusive environments and from the nomadic life that may ensue. Many develop the same problems that plague abused adults: PTSD, anxiety, depression, suicidal thoughts. Male children are at greater risk of committing a violent offense if they have a history of abuse or neglect; female children who have been sexually abused are twice as likely as nonabused children to be abused in adulthood by their partners.

As more research emerges, the social implications of violence against women are becoming increasingly apparent. The circle of violence set in motion in the home moves out onto the streets and then back into homes, ruining the childhood of another generation and setting the stage for the perpetuation of all forms of violence and abuse. Violence against women is not a discrete phenomenon but one that underlies many aspects of our culture. It is time it was addressed as such. SA

LISA A. MELLMAN is an associate clinical professor at Columbia University, where she is also the associate director of residency training. Mellman directs the psychotherapy clinic for training and research at the New York State Psychiatric Institute.

The Department of Health and Human Services has a nationwide, 24-hour domestic violence hotline: 800-799-SAFE.

Women and Alcohol


JACKIE LORENTZ

Sharon Wilsnack, Ph.D.

Women tend to drink less than men do, but alcohol can affect them more strongly—and not just because of differences in body size. ***SHARON WILSNACK, Ph.D.,*** *of the University of North Dakota School of Medicine and Health Sciences, discusses the topic of women, alcohol and alcoholism with* ***MIA SCHMIEDESKAMP,*** *special correspondent for* SCIENTIFIC AMERICAN.

Q Which women are most at risk for alcoholism?

A About 4 percent of women in the U.S. abuse or are dependent on alcohol; these are women who are physically addicted to alcohol or who suffer negative social or personal consequences because of their drinking patterns. We know that heredity accounts for some of this problem drinking: women whose close relatives abuse alcohol are more susceptible to alcoholism than average, and studies of twins and adopted children have shown that this is partly because of their genes. But genetics do not tell the whole story. Many environmental factors also correlate with problem drinking in women. These include physical or sexual abuse in childhood, involvement with a partner who drinks heavily, social isolation and dependence on other substances. Women who suffer from depression or anxiety are also at increased risk for alcohol abuse, as are bulimic women and women experiencing chronic sexual difficulties, such as inability to reach orgasm.

Young women experience drinking-related problems at particularly high rates. Nearly 10 percent of women between the ages of 18 and 29 abuse or depend on alcohol, compared with only 0.3 percent of women older than 65. And young women are especially prone to episodes of heavy drinking—putting them at increased risk of engaging in drunk driving and becoming victims of violence, including sexual assault.

Do women handle alcohol differently than men?

We know that women become more intoxicated than men when they consume equal amounts of alcohol, even when we adjust the dose for differences in weight. One reason for this variation is that women have more fatty tissue than men do. Fatty tissue contains less water than muscle does, so women typically have less body water available to dilute alcohol.

In the past few years we have learned that women also metabolize alcohol differently. The activity of a key gastric enzyme that degrades alcohol—alcohol dehydrogenase—is lower in women than in men, allowing more alcohol to pass through the stomach and enter the blood. The resulting disparity in blood alcohol levels may explain why women are more vulnerable to several tissue diseases, including liver disease. Current guidelines for safe levels of alcohol consumption reflect these differences, recommending that women consume on average no more than one drink per day and men no more than two.

What impact does alcohol have on women's health?

Women who are alcoholics die at higher rates than male alcoholics with the same drinking habits. In particular, women are more likely to develop alcoholic hepatitis and cirrhosis of the liver, and their liver disease seems to progress especially rapidly. Women are also more susceptible to alcohol-related cardiomyopathy, a weakening of the heart muscle. And recent studies have found that breast cancer risk increases by 41 percent in women who consume two to five drinks per day and by 9 percent in women who have a bit less than one drink per day.

We know that alcohol raises estrogen levels in women; this rise may account for the link between alcohol consumption and breast cancer. Enhanced estrogen levels may also explain some of the health benefits of alcohol, including protective effects against osteoporosis and heart disease. But this protection seems to level off at a drink or so a day. Women who drink heavily are actually at increased risk for osteoporosis, and they may face early menopause.

Chronic, heavy drinking during pregnancy can lead to fetal alcohol syndrome, a cluster of severe physical and neurological birth defects. We have also identified more subtle alcohol-related behavioral problems in the children of women who report consuming as little as one drink per day while pregnant. Current guidelines recommend that women abstain from drinking during pregnancy, because no studies have established a safe upper limit for their drinking.

What treatments are useful for alcoholics?

The news here is positive: the great majority of problem drinkers, both women and men, do better once in treatment. For women, the key is addressing a wide range of life issues that tie into alcohol abuse, including sexual abuse and violence, relationship and job problems, and child rearing. Several medications can also help, including drugs that reduce cravings, such as naltrexone, and deterrents such as Antabuse.

What health issues should light drinkers be aware of?

Women should remember they are more sensitive to alcohol than men. Although they might be tapped to drive because they have had less to drink than their male companions, their driving skills might be just as impaired, if not more. Many medications have sedative effects or undesirable interactions with alcohol—antihistamines are a prime example. Anyone taking these should avoid alcohol. Finally, an amount of alcohol that is safe for a woman may be risky for her fetus. Any woman who might become pregnant should keep this in mind. SA

For more information, contact the National Clearinghouse for Alcohol Information at 800-729-6686.

Bad Day at the Office?

J.W. STEWART

Research shows that stress on the job affects women and men differently

by Lisa Silver, *special correspondent*

During World War II, women flocked to the workplace, and like the newsreel heroine Rosie the Riveter, they flourished. Today the world is not at war, but for many working women, it often feels that way. With its increased job demands and longer shifts, the workplace has become a source of both physical and emotional strain. Researchers have long known that work-related stress can harm your health. What they're now discovering is that stress affects women and men differently. Whereas more men than women suffer from elevated blood pressure on the job, more women suffer from repetitive strain injuries, irritable bowel syndrome, headaches, anxiety and depression. Fortunately, a range of treatments could offer help for working women.

Repetitive strain injuries (RSIs)—hand, arm and shoulder disorders marked by numbness and severe pain—make up 60 percent of all occupational illnesses, according to recent data from the Bureau of Labor Statistics. And women are the hardest hit: women with RSIs outnumber men three to one.

Why? Explanations once included differences between men's and women's strength and size. Now research suggests it is related to the jobs many women hold—namely, jobs requiring repetitive hand motions such as typing or price scanning.

Furthermore, a worker's susceptibility to RSIs depends not only on what job she has but also on how she does it. Michael Feuerstein and his colleagues at the Uniformed Services University of the Health Sciences studied two groups of computer users to see how forcefully they pounded their keyboards. The first group had severe carpal tunnel syndrome, a common RSI; the second had less severe symptoms. Feuerstein's team found that all the workers who used excessive force while typing aggravated their condition. And although the workers with less severe symptoms hit the keys more gently, they still used four to five times more force than necessary.

Why all this keyboard bashing? "It could be an indicator of stress, brought on by too much work in too little time," Feuerstein says. Adjustable keyboards may help, he remarks, and so might stress-management programs.

Figuring out how best to manage workplace stress could help women with other ailments as well. For instance, three times as many women as men report symptoms of irritable bowel syndrome, a disorder marked by intestinal pain and abnormal bowel movements. Although stress does not cause irritable bowel syndrome, it can trigger it, says Marvin M. Schuster of the Johns Hopkins University School of Medicine.

Anyone who has had butterflies before an important meeting knows there certainly is a relation between mind and gut; for sufferers of irritable bowel syndrome, the connection may simply be tighter, Schuster says. Citing a recent study conducted at the University of California at Los Angeles, Schuster explains that in healthy people, stress activates a region of the brain that helps to calm the body down. In people with irritable bowel syndrome, however, stress activates a region that controls the body's vigilance and fear responses.

Thus, during stressful times, patients' sensory nerves are on high alert, causing them to experience intestinal sensations more acutely, Schuster explains. New Prozac-like drugs might help, he says, by blocking the reuptake of serotonin, the neurotransmitter involved in, among other things, pain perception. Dietary changes, such as eating more fiber and less gas-producing food, may also help.

Job-related stress appears to play a role in another common ailment seen in working women: headaches. Researchers at the Johns Hopkins University School of Public Health recently found that women are 15 percent more likely than men to have tension headaches. Especially at risk are highly educated women ages 30 to 39.

Female hormones may explain the gender difference but not why headaches cluster in certain women, says Brian S. Schwartz, the study's lead author. "No one knows the cause of tension-type headaches," he comments. "But we found they increased dramatically with education and plateaued during the prime working years. Both these facts suggest that something at work is contributing." Peering at the computer for hours and increased job demands could be factors, he speculates.

These same factors may have psychological effects as well. In a study of female clerical workers, researchers at Duke University found that women who reported high job strain—defined as heavy workload and low decision-making opportunities—suffered more from anxiety and depression than women with manageable workloads and more job control. Similar studies of men found no connection between workplace stress and mood disorders, says Redford B. Williams, who led the Duke study.

One reason may be the dual roles women occupy, Williams notes. "Women do the lioness's share of work," he points out. "When work at home is factored in, a woman's workweek is on average 15 hours longer than a man's." More flextime and stress-management training may be a remedy, he suggests.

Another solution may lie in changing a woman's "second" job—the home. "Women aren't unwinding after work," says Gary D. James of Cornell University Medical College. Citing a Swedish study that looked at male and female workers at a Volvo factory, James states that men's stress hormones and blood pressure rise at work, then fall at home. With women, the opposite is true. Indeed, for some women, the levels never fall. "And once you add children into the equation, women's blood pressure and stress hormone levels are elevated even more," he says.

So what's a working woman to do? "Try to get your husband to share more of the work at home," Williams urges. A prescription, he admits, that may or may not be so easy to fill. SA

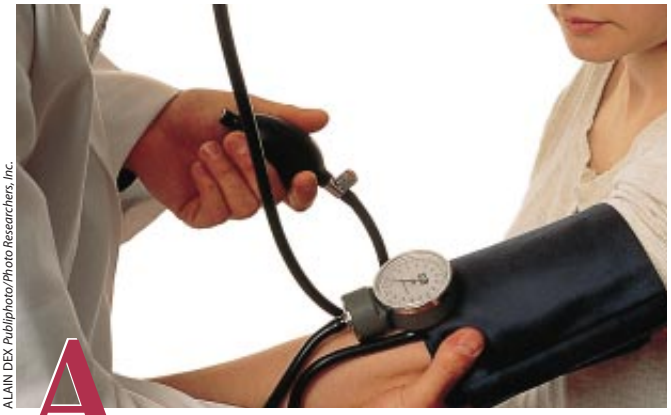
PHOTOGRAPH BY JAYNE WEXLER; HAIR AND MAKEUP BY LANA GERSMAN; BACKDROPS BY CHARLES BRODERSON

Many of the 25 million U.S. women in their 50s and 60s are facing chronic illness—such as diabetes, hypertension or arthritis—for the first time.

50s and 60s

FACT SHEET

What women in their 50s and 60s need to know



ALAIN DEX *Publiphoto/Photo Researchers, Inc.*

After menopause, a woman's risk of having a heart attack begins to rise; her risk peaks during her late 60s or 70s, when estrogen levels have been declining for over a decade. One in five women over age 65 develop some form of **heart disease.** The American Heart Association (AHA) reports that 44 percent of women who have a heart attack die within a year, compared with only 27 percent of men. Watch your blood pressure and cholesterol level, exercise regularly and monitor your intake of fat—the AHA recommends a diet that derives no more than 30 percent of its calories from fat.

If you're thinking about having a facelift to get rid of those encroaching **wrinkles,** be prepared to spend close to $5,000 and several weeks recovering. For more information, visit the American Society of Plastic and Reconstructive Surgeons at http://www.plasticsurgery.org on the World Wide Web.

BILL CARDONI *Liaison International*

Cancer of the endometrium, the lining of the uterus, is the most common cancer of the female reproductive system in the U.S. The average age at diagnosis is 60. It is sometimes detected by a Pap smear, but there is no specific screening test that can catch it early. If you didn't begin menopause until after age 52, are overweight or have never been pregnant, you have a higher risk of developing endometrial cancer. Ask your doctor what symptoms to watch for.

Too tired? According to the National Sleep Foundation, Americans sleep, on average, 20 percent less than they did a century ago. Lack of sleep accumulates, resulting in depression, low energy and eroded health.

A NEW TEST FOR OSTEOPOROSIS was approved by the Food and Drug Administration in March. The test uses ultrasound to detect the loss of bone density characteristic of osteoporosis. The new devices are expected to be smaller and cheaper than current technology, which relies on x-rays of the hips, spine or wrist.

Some 8.1 million women in the U.S. are diabetic (that's just over 8 percent of all women); most of these women are older than 45. **Diabetes** *is one of the top 10 causes of death in the U.S. Diabetic women of any age have more than twice the risk of heart attack than nondiabetic women.*

There were
20 million
women aged 65 and older in the U.S. in 1996.
(Bureau of the Census)

The average age of menopause in America is 51. You can still become pregnant during menopause. Only after you've gone through a full year without a menstrual cycle can you be certain you are no longer fertile.

CHECKUP

Essential medical exams for women in their 50s and 60s

HEART DISEASE SCREENING

Heart disease is the number-one killer of women in America. Make sure you have your blood pressure and cholesterol checked during regular checkup visits. If further screening is necessary, your doctor may recommend other tests, such as an electrocardiogram, which evaluates the activity of the heart muscle.

COST: Blood pressure test included in a routine visit to the doctor; cholesterol test $20–$35; electrocardiogram $40–$90

COLORECTAL CANCER SCREENING

When women hear "cancer," they often think only of breast cancer. But the American Cancer Society (ACS) estimates that in 1998 colorectal cancer will kill 24,600 women in the U.S., and 90 percent of people usually diagnosed with this cancer are older than 50. In addition to having a rectal exam during your annual trip to the gynecologist, you should have a fecal occult blood test (in which your doctor checks for blood in a stool sample) every year after you turn 50, according to the ACS. The ACS also suggests a sigmoidoscopy (in which the doctor inspects your lower large intestine for precancerous growths) every five years. In some cases, your doctor might recommend a colonoscopy, which will allow her to examine the entire large intestine.

COST: Fecal occult blood test $20–$30; sigmoidoscopy $200–$300; colonoscopy $1,300–$1,400

BETH PHILLIPS

A recent study published in the *Journal of the American Medical Association* revealed that taking in more ***folate***—in food or from supplements—can help women reduce their risk of coronary heart disease. The results suggest that any increase in folate intake will help lessen the risk of heart disease, but your best bet is to have a daily intake of at least 400 micrograms.

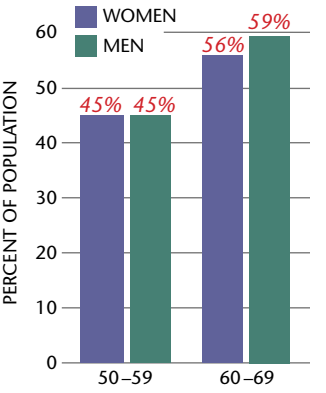
Risk of Developing Breast Cancer in the Next Year

Age	Risk
50–54	1 in 450
55–59	1 in 386
60–64	1 in 292
65–69	1 in 244

(National Cancer Institute)

CHRIS PRIEST SPL/Photo Researchers, Inc.

ESTIMATED PREVALENCE OF CARDIOVASCULAR DISEASES IN THE U.S.



SOURCE: 1998 Heart and Stroke Statistical Update, *American Heart Association*

October is National Breast Cancer Awareness Month. Many facilities lower mammogram fees, extend their hours and offer special classes during this time. Watch for flyers and take advantage of the opportunities.

Feeling low? Some 20 percent of women in the developed world suffer from **DEPRESSION.** If you are diagnosed with depression, your doctor can prescribe antidepressant medication or refer you to a psychotherapist. For more information about depression, call the National Foundation for Depressive Illness at 800-248-4344.

MAMMOGRAM

There's not nearly as much controversy about mammograms for women in their 50s and 60s as there is for younger women: both the American Cancer Society and the American Medical Association recommend annual mammograms after you turn 50; the National Cancer Institute (NCI) recommends being tested once every one to two years. False positives can still be problematic, however: the NCI reports that 86 percent of American women older than 50 who have had abnormal mammograms received at least one false positive result.

COST: $50–$150

PELVIC EXAM AND PAP TEST

Over half the women older than 55 do not have annual Pap tests, yet 60 percent of cervical cancers are diagnosed in women of this age group.

COST: Pelvic exam $40–$100; Pap test $20–$60. Usually covered by insurance.

HEARING TEST

Loss of hearing as people grow older is completely natural, and although there is no way to stop the process, your doctor may still be of some help. Your regular physician can determine the physical cause of hearing loss and may refer you to a specialist if necessary. A hearing aid will amplify sounds entering your ear and will reduce stress on your aging inner ear. Have your hearing tested immediately if you suspect hearing loss. To find a hearing specialist in your area, call the American Speech-Language-Hearing Association at 800-638-8255.

COST: $10–$100

BONE DENSITY EXAM

One out of every two women older than 50 fractures a bone made brittle from the onset of osteoporosis, a disease characterized by loss of bone density. A doctor can x-ray your hips, spine or wrists with low-level radiation to detect bone loss and recommend hormone therapy or other drugs, diet changes or exercise to increase the mass and strength of your bones. Ask your doctor when and how often you should have your bone density measured.

To learn more about osteoporosis prevention and treatment, visit the National Osteoporosis Foundation at http://www.nof.org on the World Wide Web. To find a bone-density testing location in your area, call the National Osteoporosis Foundation's Official Action Line at 800-464-6700.

COST: $100–$300. Medicare pays in some states. But beware, not all private insurers will cover this test; ask before you go to the doctor.

EYE EXAM

Is your vision blurry or spotty? Many symptoms of eye disease and loss of vision are not apparent until conditions such as glaucoma or cataracts become more advanced. Glaucoma, for example, is one of the leading causes of blindness in the U.S. and occurs most often in people over 40; cataracts are most common in people over 55. The American Optometric Association recommends an eye exam at least every two years for adults between the ages of 41 and 60. After age 60 you should have your eyes examined annually.

Treatment can slow or stop eyesight loss, and taking care of your eyes now can help prevent problems later. Make sure you have plenty of light when reading and wear sunglasses that block ultraviolet radiation when you are outdoors.

COST: $50–$100

COMPILED BY STEPHANIE J. ARTHUR AND KRISTA MCKINSEY; GRAPH BY LAURIE GRACE

J. W. STEWART

Menopause and the Brain

New studies suggest that the brain may be an important player in the timing of menopause

by Phyllis M. Wise, Ph.D.
University of Kentucky

A regular menstrual cycle is like a well-oiled machine. Each component must move in time with and match the rhythms of the others. Similarly, hormones in the body that control the menstrual cycle must be released with accurate timing, in the right amounts and in the proper locations. If the rhythms or fine-tuning falls out of step just slightly, menstruation becomes irregular or even stops.

Menopause marks a permanent end to a woman's natural menstrual cycle; on average, women in the U.S. cease menstruating around the age of 50. With increasing numbers of women living into their 70s, 80s and beyond, it is essential that researchers gather reliable and detailed information about what happens before, during and after menopause.

Certain facts have become clear concerning what happens to women after menopause. For instance, levels of the female hormone estrogen fall off; this decline has been linked to an increased risk among postmenopausal women for osteoporosis, heart disease and possibly even Alzheimer's disease.

But what about before and during menopause? Scientists have long recognized that fertility gradually declines among women starting in their mid-30s, as the number of follicles (the structures in the ovary that contain developing eggs) dwindles. Simultaneously, women's hormone levels start to fluctuate wildly: while estrogen drops off, levels of other hormones involved in a woman's reproductive cycle, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), begin to soar.

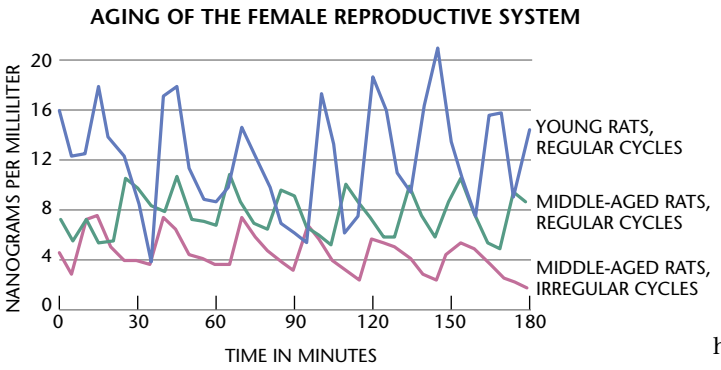
Menopause was once thought to occur when the ovaries ran out of eggs. But hormonal signals from the brain may prompt the end of a woman's menstrual cycles.

For many years, scientists accepted the view that menopause results simply from the gradual exhaustion of the supply of follicles in a woman's ovaries and that the associated hormonal changes are simply side effects of aging ovaries. More recently, however, researchers have begun to question this simple notion and to propose an alternative hypothesis: menopause may result in part from the aging of the brain.

The Aging Ovary

The original concept that aging ovaries are the primary cause of menopause derives from the fact that female mammals are born with a large, but finite, nonrenewable reserve of dormant follicles. (This situation stands in contrast to male mammals, which continually regenerate their supplies of sperm.) The number of follicles in a woman's ovaries is set during fetal development; once the supply is exhausted, menstrual cycles stop and a woman can no longer become pregnant unless she receives a donor egg. Females are born with, on average, about half a million dormant ovarian follicles, but the vast majority of these perish before they have a chance to mature. During a woman's life, these follicles are constantly reawakening and entering the growing pool of follicles, but only a minute fraction—less than one tenth of 1 percent on average—complete the path to ovulation, in which an egg is released from the ovaries ready for possible fertilization.

A woman's body regulates the development of the egg inside the follicle by an elaborate biochemical process. Briefly, at the start of the menstrual cycle, the hypothalamus (located at the base of the brain) produces carefully orchestrated pulses of the compound gonadotropin-releas-



LAURIE GRACE; SOURCE: K. SCARBROUGH AND P. M. WISE

The pattern of secretion of luteinizing hormone, a reproductive hormone released from the pituitary, becomes erratic with age. The author measured levels of LH in laboratory rats for three hours and found that in young rats (blue) *the pulses of LH were quite large; however, as the rats aged* (green) *and their reproductive cycles became irregular* (red)*, the pulses of LH became smaller. A similar pattern can be seen in women approaching menopause.*

ing hormone (GnRH). These pulses of GnRH in turn stimulate the pituitary (which protrudes from the base of the brain) to secrete LH and FSH, in another precisely timed pattern. The exact pattern of LH and FSH secretion determines the rate and number of follicles that will undergo the final stages of maturation.

Some scientists have hypothesized that to maintain a constant stream of ripening follicles, the ovaries must contain an enormous excess of dormant follicles waiting to mature. It turns out that some of the hormones required to promote the growth of a follicle—such as estradiol (a form of estrogen), activin, inhibin or other growth factors—are actually released by other, maturing follicles. So as the number of follicles drops over a woman's lifetime, levels of these crucial compounds fall off as well. As a result, not only are there fewer follicles around to start developing as a woman ages, but even fewer of the ones that do start will be able to mature fully.

After a woman reaches age 35, the rate at which her follicles die increases dramatically; scientists don't fully understand why. But many investigators believe the rate of the loss begins to accelerate when the number of follicles in a woman's ovaries drops below a critical threshold; below this point, the hormonal fine-tuning necessary for the other follicles to mature is so disrupted that more and more follicles die during the growth and maturation process. In short, the loss of follicles becomes a self-perpetuating cycle—as follicles die, the ones left behind die even more rapidly. Eventually, by age 50 or so, all of a woman's ovarian follicles are gone, and her menstrual cycles cease for good.

The Aging Brain

The line of reasoning I outlined above focuses on events taking place in the ovaries. For the past 20 years, I have been looking to the brain to understand what happens as the reproductive system ages and ultimately ceases to function. Because, as I described earlier, the brain plays such a critical role in a woman's menstrual cycle, it makes sense that the aging brain would play a role in menopause as well.

Several investigators, including Dennis W. Matt of Virginia Commonwealth University, Joseph Meites, a professor emeritus at Michigan State University, and myself, have described the hypothalamus as the possible pacemaker of menopause. We contend that the increased loss of ovarian follicles observed after age 35 could be caused not by aging ovaries but by alterations in the secretion of hormones from the brain. In particular, I suspect that changes in the patterns of the signals governing the release of GnRH from the hypothalamus play an important part in the process. Although we do not know precisely what controls the release of GnRH, it appears that many factors are involved, including compounds such as norepinephrine, dopamine and serotonin, all of which perform numerous tasks throughout the brain. Intriguingly, other signs of menopause, such as hot flashes and sleep disturbances, may result from normal, age-related deterioration of the hypothalamus.

To test the hypothesis that the timing of menopause is dictated by the brain, scientists need to determine whether and how GnRH levels shift in postmenopausal women. Because most reproductive hormones normally fluctuate not just over the course of a woman's monthly cycle but also over the course of a single day, it would be ideal to measure the amount of GnRH in the blood samples of a group of women every few minutes over a period of a day and to repeat the sampling every several weeks for three to five years, beginning as soon as the women show any signs of approaching menopause. (This time is known as the perimenopausal period and typically begins in a woman's late 30s or early 40s.)

Unfortunately, though, there are no tests currently available that are sensitive enough to detect GnRH in the blood, so investigators, including Dennis Matt and Nancy E. Reame of the University of Michigan, have instead measured LH, which can be detected in the blood and which serves as an indirect marker for GnRH. (Recall that when the hypothalamus secretes GnRH, the pituitary responds by releasing LH as well as FSH.)

These researchers tested perimenopausal women every five to 10 minutes for several hours on different days of their menstrual cycles. Some of the women were still experiencing regular cycles; others were more irregular. In this way, the scientists were able to monitor LH pulses as well as levels of other critical reproductive hormones, such as estradiol, progesterone and inhibin, for women in different stages of the menopausal transition. In another approach, Nanette Santoro of the University of Medicine and Dentistry of New Jersey took urine samples to assess how estradiol levels change in perimenopausal women. (Urine tests have one big advantage—because they are noninvasive, data can be collected for longer intervals.)

Hormonal Fluctuations

The outcome of these studies has been revealing. Typically in young women, the pituitary pumps out LH in very predictable, rhythmic pulses. But, as Matt has shown, among women between the ages of 40 to 45 who still exhibit menstrual cycles of normal length, the release of LH becomes erratic, consisting of longer but less frequent pulses, indicating that the hypothalamus is sending out irregular pulses of GnRH. Women approaching menopause also have an unusually high level of FSH during the early part of their menstrual cycles; this condition can result not just when levels of inhibin are low (the standard explanation) but also when the hypothalamus sends out very low levels of GnRH or when the pulses of GnRH are some-

how altered from their typical frequency.

My colleagues and I at the University of Kentucky are studying laboratory rats to find out more about how the activity of chemicals in the brain changes with age. In particular, we hope to learn more about what regulates the release of GnRH from the hypothalamus. We chose to work with rats because this species has already taught scientists a great deal about many aspects of human reproduction, including puberty, ovulation, pregnancy and lactation. Although there are differences among species, there are also many important common features.

For instance, the pathways by which the hypothalamus controls the ovaries are quite similar in both rats and humans. We have found that in middle-aged female rats that are still regularly cycling, there are measurable changes in the release of LH from the pituitary, analogous to the changes seen in middle-aged women approaching menopause.

Furthermore, we have found correlating variations in the levels of specific compounds in the brain, such as norepinephrine, serotonin and beta-endorphin, suggesting that these chemicals, which control GnRH, may cause the changes in LH secretion that we observe in aging rats. We have also observed changes in the activity of the nerve cells in the brain that modulate the release of GnRH, suggesting that the ability of these neurons to function correctly might be deteriorating with age.

I mentioned earlier that the menstrual cycle relies on the interplay of hormones and other compounds that all must function in tempo with one another. Indeed, GnRH, LH and FSH are just a few of the players involved in a woman's reproductive system. And as a woman ages, the coordination between these hormones and the neurotransmitters in the brain, such as norepinephrine, dopamine and serotonin, gradually deteriorates. The effects—hormones being secreted in the wrong amounts or at the wrong times—are quite subtle at first; indeed, they may not even show up in average measurements of a menopausal woman's hormones, but only in daily or even hourly readings.

Eventually, though, the release of crucial reproductive hormones from the brain becomes completely unsynchronized; the changing levels of hormones such as FSH and LH then interfere with the proper development of ovarian follicles, leaving more and more of them to perish. Finally, a woman's regular menstrual cycle ceases completely.

Your Biological Clock

So what's going on in the brain as women grow older? Why does the timing of hormone secretion become so erratic? The adage about the ticking of your biological clock may not be too far from the truth. A region of the hypothalamus known as the suprachiasmatic nucleus serves as the body's internal clock, regulating a variety of functions, such as sleep, that each have their own 24-hour cycle. (Body temperature also typically follows a daily cycle—you cool down at night and warm up through the day.)

THE MORE WE LEARN ABOUT WHAT HAPPENS BEFORE AND DURING MENOPAUSE, THE MORE CHOICES WOMEN WILL HAVE WHEN CONFRONTING THEIR HEALTH CONCERNS AS THEY GROW OLDER.

The secretion of virtually all hormones fluctuates throughout the day as well. I suspect that parts of the body's internal clock deteriorate with age, causing the release of hormones to become gradually unsynchronized. This hypothesis is bolstered by the observation that other daily rhythms known to be controlled by the suprachiasmatic nucleus are also thrown off as people age: for instance, older women (and men) tend to get up earlier, go to bed earlier and sleep for shorter stretches.

The suprachiasmatic nucleus does not work in a vacuum, however. Many other parts of the body communicate with it and convey information about the environment, largely through the neurons that interconnect the entire central nervous system. For example, when we fly to Paris, our biological clock shifts because of environmental cues, such as when the sun rises and when we eat meals. In older people, the suprachiasmatic nucleus does not seem to work as well: for instance, our so-called free-running period, which is, in effect, what the body recognizes as one day, grows shorter (hence the altered sleeping patterns), and our ability to respond to environmental signals also deteriorates.

Scientists are still studying what prompts these changes. Perhaps they reflect aberrations in the suprachiasmatic nucleus itself, or perhaps the neurons that communicate with the suprachiasmatic nucleus become altered with age. How does all of this affect a woman's menstrual cycle? I believe that as the ability of the suprachiasmatic nucleus to tell time diminishes, vital neurochemical signals from the body's internal clock to the neurons in charge of GnRH release become desynchronized, gradually disrupting the pattern of hormone secretion from the brain.

Researchers in my lab and elsewhere are only beginning to unravel the biological processes—both in the brain and in the ovaries—that control menstruation and menopause. The more we learn about what happens before and during menopause, the more choices women will have when confronting their health concerns as they grow older. For example, patients and physicians alike wonder about the risks and benefits of hormone replacement therapy for menopausal and postmenopausal women. A deeper understanding of the biochemistry of menopause might enable scientists to produce other options beyond estrogen with the benefits of today's therapies but not the risks.

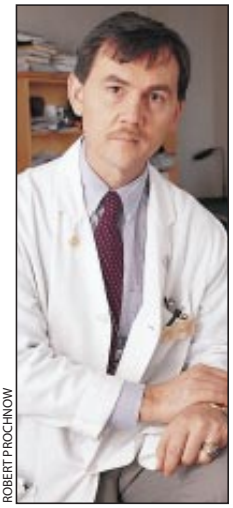
Better options for hormone replacement therapy are particularly important because we and other investigators have found that when estrogen levels are low, as they are after a woman goes through menopause, the brain and other organs are particularly vulnerable to injury. This occurrence may explain why postmenopausal women suffer from increased incidences of stroke, Alzheimer's disease, heart disease and problems in cognitive function. Ultimately, a richer awareness of how the brain ages will benefit both women and men. SA

PHYLLIS M. WISE is professor and chair in the department of physiology at the University of Kentucky. Her long-term interests focus on the role of the brain in menopause and the repercussions of prolonged diminished estradiol levels that characterize the postmenopausal period.

Q&A

Hormone Replacement Therapy

Rogerio A. Lobo, M.D.



ROBERT PROCHINOW

JESSICA BOYATT

Graham A. Colditz, M.D.

As women of the baby boom generation are all too aware these days, bodies start to change after 50. After a long career of producing eggs and estrogen, the ovaries take an early retirement, and the body goes through the hormone withdrawal process—hot flashes and all—known as menopause.

To many women, living with little estrogen is an unappealing prospect, so every year doctors write about 60 million prescriptions for the hormone. Although no other drug is more widely prescribed in the U.S., scientists still debate the risks and merits of hormone replacement therapy. That debate is taken up here as ***REBECCA ZACKS,*** *special correspondent for SCIENTIFIC AMERICAN, talks with two experts in women's health:* ***ROGERIO A. LOBO, M.D.,*** *and* ***GRAHAM A. COLDITZ, M.D.*** *Lobo is the chief of obstetrics and gynecology at Columbia-Presbyterian Medical Center and a self-proclaimed advocate of estrogen, which he recommends regularly in his capacity as head of the hospital's Menopause Treatment Center. Colditz, an epidemiologist at Harvard Medical School, is an outspoken critic of estrogen therapy. He has investigated its effects while working as a lead researcher on the Nurses' Health Study, which has been following more than 120,000 American women since 1976. Although Lobo and Colditz agree on many of the basics about estrogen, when it comes to the connection between estrogen therapy and cancer, they just don't see eye to eye.*

Q *What are the hormones in "hormone replacement therapy"?*

A **LOBO:** Estrogen is the mainstay. There are many dosages and different forms, from synthetic to natural, given as oral formulations or through skin patches. It can also be administered vaginally.

COLDITZ: More recently, there's been growing use of progestin along with the estrogen, particularly among women who still have their uterus, to counter the risk of getting uterine cancer. Taken alone, estrogen increases a woman's risk of uterine cancer fourfold to sixfold. And, like estrogen, there are a number of different formulations of progestin on the market.

Why do some women decide to try hormone replacement therapy as they enter menopause?

COLDITZ: Traditionally, the major reason for use has been relief of menopausal symptoms—preventing hot flashes and other problems. More recently, there's been a push to consider the decrease in bone density associated with menopause as an indication for starting estrogen at the time of menopause to prevent loss of calcium and ultimately to prevent osteoporosis. Also very recent is the notion of using hormones for preventing heart disease. And so some women may be advised to take hormones for the preventive benefit, not just for the relief of menopausal symptoms.

Why do other women choose not to use hormones during menopause?

COLDITZ: There's a huge spectrum of reasons. There's one extreme of a woman who doesn't want to take any unnecessary hormones or drugs or to put anything in her body that she doesn't need to. There's the attitude "If I'm not having symptoms, why should I take a drug?" And some women really don't tolerate estrogen plus progestin. They get premenstrual symptoms, and when you've not had them for 10 years, you don't sign up to take a pill to induce symptoms on a monthly basis.

If a woman goes through menopause without using hormones, why might she still choose to begin replacement therapy later in life?

LOBO: If we take an extreme—a woman with a strong family history of both osteoporosis and cardiovascular disease and, for the sake of argument, no history or risk factors for breast cancer—then I think she is a very good candidate for estrogen in her later years.

COLDITZ: Again, there's been a shift in philosophy as we've moved from use of hormones primarily for relief of menopausal symptoms, such as hot flashes and vaginal dryness, to use of hormones long term for prevention.

What concerns women most about taking hormones?

LOBO: The overriding risk that concerns women is that of breast cancer. The perception is that most women die of breast cancer and that only a few die of cardiovascular disease. But the lifelong mortality related to breast cancer is about 3 percent, and for cardiovascular disease it's in the range of about 30 percent. It's actually the reverse of what women perceive.

COLDITZ: My sense is that women are most concerned about the risk of cancer. Even though the evidence that estrogen causes breast cancer—evidence that is now quite powerfully conclusive—has not yet fully reached women and the clinicians prescribing the hormone, it is clear that women are particularly concerned about breast cancer.

The Benefits of Hormones

You mentioned that estrogen helps to prevent osteoporosis in postmenopausal women. How does it do so?

COLDITZ: In a simple sense, estrogen works to prevent osteoporosis by stimulating cells in the bone to maintain their function to retain calcium and to maintain the actual structure of the bones, keeping them strong and thereby reducing the risk of breaking bones.

So how much protection does estrogen provide for a woman's bones?

LOBO: If you're talking about hip fractures, it's probably in the range of about a 50 percent reduction of fracture risk—I mean that's the bottom line.

Let's turn to estrogen and cardiovascular disease. How does estrogen replacement therapy reduce a woman's risk of heart disease and heart attack?

COLDITZ: Estrogen influences cholesterol metabolism and leads to a higher HDL—the good cholesterol—and a lower LDL cholesterol, the bad cholesterol. Estrogen also causes the muscles in the artery walls to relax a little bit so blood flows better. People have studied blood flow to the brain in women exercising on treadmills, comparing women when they're taking estrogen to when they're not. And when they're taking estrogen, they can exercise longer and have better blood flow. People have also been looking at the antioxidant effects of estrogen. So those mechanisms together account for most of the protection that's seen, though probably not all of it.

How much does estrogen replacement therapy reduce a woman's risk of heart attack?

COLDITZ: We see about a 50 percent reduction among high-risk women who are currently taking hormones compared with women who have never taken them. The effect is stronger among current users than among women who have stopped using hormones. So I'd say a woman's risk of heart attack is cut in half if she's currently taking estrogen and is cut by 25 percent after she stops.

Does adding progestin to hormone therapy alter any of the cardiovascular benefits?

LOBO: This is the difference between epidemiological observational studies and clinical trials. In the former, researchers study a population of women who have decided on their own whether to take hormones and what kinds to take. In the latter, researchers randomly assign volunteer participants to a course of treatment. Most clinical trials will show what I call some attenuation, some reduction of the benefits when progestin is combined with estrogen, depending on the route of the administration, the type of progestin and the specific regimen. But observational studies have suggested that there's no reduction in benefit.

Do women need to start taking hormone replacement therapy by a certain age to enjoy the benefits of estrogen for their hearts and bones?

LOBO: There are going to be benefits whenever you start. But the benefits are going to be less, obviously, if you start later. For bone loss, it's been shown that whenever you start estrogen therapy, you can stop bone loss. The effects on cardiovascular health and cognition have also been shown to be beneficial when estrogen is taken starting at a later age. There really haven't been studies of 80-year-old women. But certainly women through their 60s and 70s benefit from starting estrogen.

COLDITZ: This is a really central question that still hasn't been answered. If you start at age 65 rather than at age 50, is the benefit still there? Because, after all, the risk of heart attack and hip fracture between ages 50 and 60 is in fact still pretty small. Because few women have started taking hormones at older ages, there's not a lot of experience yet. But the heart benefits are thought to be there for women who start hormones at older ages, and bone benefits are probably going to be there as well. They may not be as pronounced as they would be for someone who began taking hormones earlier in life, but there should still be benefits. And the upside of starting later is that there is presumed to be less cancer risk if you haven't been using the hormones for 10 or 15 years from menopause to age 60 or 65.

Once a woman has started treatment, must she continue to take hormones indefinitely?

LOBO: Yes, that's the problem. Most data would suggest that as soon as you stop taking hormones you lose the benefit. So I think that long-term therapy really is better. But of course the

Guide to Estrogen and Progestin Use

If you are considering hormone replacement therapy and you have had a hysterectomy, you should take estrogen alone. You and your doctor can choose from the following options:

Pills
Estrace (*estradiol*)
Estratab (*sterified estrogen*)
Menest (*esterified estrogen*)
Ogen (*estropipate*)
Ortho-EST (*estropipate*)
Premarin (*conjugated equine estrogen*)

Patches
Alora (*estradiol*)
Climara (*estradiol*)
Estraderm (*estradiol*)
Fempatch (*estradiol*)
Vivelle (*estradiol*)

Vaginal Ring
Estring (*estradiol*)

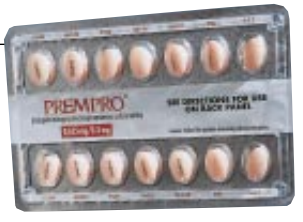
If you have not had a hysterectomy, you should take progestin with your estrogen. Ask your doctor about the following choices:

Pills
Aygestin (*norethindrone acetate*)
Cycrin (*medoroxyprogesterone acetate, or MPA*)
Prometrium (*micronized progesterone*)
Provera (*MPA*)

Vaginal Gel
Crinone (*micronized progesterone*)

If you have not had a hysterectomy, you can also ask your doctor about taking a combination of progestin and estrogen:

Pills
Premphase (*conjugated estrogens and MPA*)
Prempro (*conjugated estrogens and MPA*)



If your primary concern is osteoporosis, you can consider a selective estrogen receptor modulator (SERM):

Pill
Evista (*raloxifene*)

PHOTOGRAPHS BY BETH PHILLIPS

risks are related to the duration of use. So that's the dilemma.

COLDITZ: Historically, most women took their hormones for relief of symptoms during menopause and then stopped. The still unanswered question is: Can you take hormones short term for relief of symptoms at menopause, stop and then maybe 15 years later start again to get the preventive benefits when the risks of heart disease and bone fractures are big enough to justify the potential increased breast cancer risk?

Estrogen and Breast Cancer

There is so much controversy surrounding the impact of estrogen on a woman's risk of breast cancer. How has this been studied, and why do the data often seem to conflict?

LOBO: Well, it's been studied for 20-plus years, and it's been studied primarily in epidemiological trials. And there's no clear-cut association—at least in my view. That's largely because if there is a risk, the risk is relatively small. The fact that we really haven't completely figured this out in over 20 years of research shows that if there is an association, it is so small that it's very hard to prove statistically, unless you have a large number of women. And once you start looking at large numbers of women, then you have so many confounding variables: biases inherent about why these women are taking hormones to begin with, what the characteristics of the group are and so forth.

COLDITZ: Probably most of the literature on this question to date has had troubles with the precision of the analysis. At any given age, the earlier a woman went through menopause, the longer she is likely to have been using hormones. Which then comes back to a basic factor that has in large part been ignored. Since the 1950s we've known that a woman's age at menopause is a strong predictor of her risk of breast cancer: that the earlier a woman went through menopause, the lower her lifetime risk of breast cancer. So we have to control statistically for age at menopause when we start looking at use of hormones. And if we don't control tightly, then we start to mix up the effect of age of menopause and the effect of hormones. Some of the controversy really came from different studies using different techniques of analysis—some of which may control for age at menopause more tightly than others—and so they get different results.

In part, this controversy is fed by the groups who are pro-estrogen picking out studies that didn't find any adverse effect and ignoring the total body of evidence. And then I suppose it's fed by people like me on the other side saying it's unarguable now that estrogen causes breast cancer and therefore we really need to stop and think before we go willy-nilly prescribing a drug that's clearly going to cause cancer.

So in your interpretation of the data, how much is a woman's risk of getting breast cancer affected by estrogen replacement therapy?

LOBO: My bottom line is that there is no definitive answer about estrogen and breast cancer. There is suggestive evidence that there is a small increased risk. If a woman happens to have some abnormal breast cells during her menopausal years, taking estrogen, particularly at high doses and for long periods, may promote that cancer to develop. Not to say that if she were 70 or 80, she might not have developed the disease anyway. So that's the way I view it. If there is an increased risk, it's in the range of about 20 percent, even up to 30 percent among

the susceptible population. It's something that's just on the borderline of being significant.

COLDITZ: Well, we have to be careful. Estrogen causes breast cancer even if a woman doesn't take postmenopausal hormones. We know that women with higher estrogen levels after menopause have a higher risk of breast cancer than women with lower levels. We know that obese women have higher estrogen levels and are at increased risk of dying from breast cancer, so there's a lot of evidence now that just natural estrogen levels are related to breast cancer risk. And we know separately from a recent study that the risk of breast cancer goes up somewhere between 2 and 3 percent for each year a woman uses hormones, which really means that after 10 years of use we're looking at around a 30 to 35 percent increase in risk compared with a woman who has never used hormones. What this translates to is that if we have 1,000 women beginning the use of postmenopausal hormones at age 50 and taking the hormones for 10 years, there are going to be six excess cases of breast cancer caused by the estrogen therapy. If the same group of women uses hormones for 15 years, there'll be 12 excess cases.

Alternatives to Estrogen

In light of the various concerns about hormone replacement therapy, researchers are trying to create other options. What are the so-called designer estrogens that are currently in development and testing?

LOBO: This is the group of selective estrogen receptor modulators, or SERMs. The prototype of this group is raloxifene, although the anticancer drug tamoxifen is actually a SERM also. It's not as glamorous, but it's really the parent of this group. These compounds selectively bind in certain tissues to have either an estrogenlike effect, known as an agonist effect, or an estrogen-opposing effect, known as an antagonistic effect. The ideal designer estrogen would be one that does not stimulate the breasts or the uterus but would have estrogenlike effects on the heart, the brain, the bones and the vagina. And to date there is no ideal designer estrogen. There may or may not ever be a completely ideal designer estrogen.

Are there other ways besides taking estrogen that women can protect themselves from osteoporosis and heart disease?

LOBO: Certainly for osteoporosis there are natural things that a woman can do that are somewhat helpful—exercise, eat a decent diet, get enough calcium—but at the next level, which is taking medication, a woman's options include alendronate, calcitonin and raloxifene or tamoxifen.

For cardiovascular disease, it's the same thing: a low-fat diet, antioxidant vitamins, exercise, not smoking—all the things we know and read about. None of them is as good as estrogen for either osteoporosis or cardiovascular disease, but there certainly is some benefit. It's better than doing nothing.

COLDITZ: In the antioxidant area, folate is at least as strong as estrogen for fighting cardiovascular disease, as is vitamin E. For a smoker, quitting smoking will actually have as big an impact as taking estrogen. So in fact there are a number of comparable strategies, and those with equal benefits and low risks should come to the top of the list of strategies. To me, that's where some of these options clearly dominate the choice of estrogen for preventing heart disease.

Many women rely on their doctors for advice about hormone replacement therapy. How well does the information that those doctors provide reflect the latest research?

LOBO: It's gotten to the point where there's more information coming from the media than from anywhere else. One of the reasons women discontinue hormones is because there's a lack of information, and they are concerned about not being counseled adequately. But I think hormone replacement is becoming such a hot topic that people are beginning to stay on top of it—both physicians and patients. I think the information trickles down much faster than it did in the past.

COLDITZ: The benefits of hormones are pretty clearly communicated out there rather quickly. The adverse effects are, shall we say, less popular. On a Saturday morning in Buffalo not that long ago, I gave a lecture for a continuing education program directed primarily at gynecologists, and after I'd given my talk, one of them said, "It's almost irresponsible of you to publish your material in the *New England Journal of Medicine* because now I have to talk to all my patients about the breast cancer risk." Well, maybe that's why we publish, you know.

Realistically, how long do you think it will be before women and their doctors have enough information to make decisions about hormone replacement therapy with confidence?

LOBO: You'll never know everything. There will always be room for new studies, new information and refinements of what we know. I feel very comfortable with what information we already have. We'll know more in the next few years. Every year brings more new information. But I really think you can synthesize what you have now and make an informed choice.

COLDITZ: With these new drugs [SERMs] coming, maybe every year we've got to sit down and reassess where we are. So even if a woman is using estrogen right now for relief of menopausal symptoms, in a year's time she might want to stop and ask, "Should I stay on this, should I be taking an alternative, what's the new evidence?" I don't know if there's one date by which we'll have the answer, because when we have the answer on drug A, drug B will have been on the market for only two years, so we'll start to have answers for it, and then drug C will just have been approved. So my attitude is this: let's not use a drug blindly for the next 10 years. Let's instead stop every year or so to reassess the approach and ask if this is the right drug, if it's the right strategy to achieve the goal, be it preventing osteoporosis or heart disease or avoiding menopausal symptoms. SA

The ongoing Women's Health Initiative (WHI) is looking at, among other issues, the risks and benefits of hormone replacement therapy. For more information about the study and the location of the nearest participating facility, call 800-54-WOMEN or write the WHI Program Office, Room 6A09, Federal Building, 9000 Rockville Pike, Bethesda, MD 20892-9110. Information about the WHI can also be found at http://www.nhlbi.nih.gov/nhlbi/whi1/ on the World Wide Web.

The National Institute on Aging (NIA) Information Center offers printed material about menopause, osteoporosis, heart disease and stroke. For more information, call 800-222-2225 (for TTY callers, the number is 800-222-4225). A variety of NIA materials are also available at http://www.nih.gov/nia on the World Wide Web.

Smoking and Breast Cancer

Cigarettes may cause more cases than the two so-called breast cancer genes combined

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National Cancer Institute

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National Center for Toxicological Research, Food and Drug Administration

Smoking has adverse health effects at any age. But new research shows that roughly half of all women are particularly prone to developing breast cancer in their 50s or 60s if they smoke.

By now, most people have heard the grim statistic of breast cancer: almost one in every eight women in the U.S. will develop the disease in her lifetime. This year alone, breast cancer will take the lives of roughly 45,000 American women.

For most women, the top risk factors for breast cancer are hormonal, such as start-

ing menstruation at a young age (before 12 years old), going through menopause late in life (after age 50), having few or no children and having a first full-term pregnancy at a late age. All these traits share one common feature: they contribute to a longer lifetime exposure to estrogen, which can spur the growth of breast cells into cancerous tumors. Estrogen levels rise at the onset of menstruation and decrease at menopause. Increasing physical activity and eating a diet rich in fruit and vegetables may decrease risk.

Family history also is an important risk factor for breast cancer. Because breast cancer is fairly common, many women have one or two relatives with breast cancer by chance. But some young women whose mother, grandmothers or sisters had breast (or ovarian) cancer carry an inherited susceptibility for the disease. Women from such high-risk families frequently carry mutations in the *BRCA1* or *BRCA2* gene. Mutations in these genes confer between a 40 and 90 percent lifetime risk of developing breast cancer. Although these familial cancer syndromes are devastating, they account for only about 5 percent of all breast cancer cases. The other 95 percent—the nonfamilial, or sporadic, breast cancers—are caused, in part, by the hormonal risk factors mentioned above and by some risk factors we are only now beginning to explore.

We believe that one important and preventable risk factor for breast cancer is cigarette smoking. Our research suggests that roughly half of all women are particularly sensitive to the carcinogens found in tobacco and so have a higher risk of breast cancer if they smoke cigarettes. Such women have a slow-acting form of a liver enzyme that normally detoxifies carcinogens. Because these women's "detox" enzymes act more slowly than the enzymes of other women, the carcinogens in tobacco last longer in their bodies, allowing the substances more time to cause cancer. For such women, every cigarette loads the dice in favor of breast cancer.

Conflicting Evidence

Epidemiologists have been intrigued for years by hints that smoking can cause breast cancer. But for every study that purports to show a link between smoking and breast cancer, others fail to demonstrate any association—and some even show that cigarette smoking decreases a woman's risk of breast cancer. This is surprising because smoking causes so many other cancers, such as lung and bladder cancer. The reason for the discrepancy might be related to a complicated interaction among unidentified chemicals present in cigarette smoke that might lower estrogen levels in the blood of some women, thereby lowering their risk of breast cancer. Smoking also appears to lower the age at which a woman goes through menopause, which would also lower breast cancer risk because estrogen levels drop at menopause.

Although many previous studies do not impli-

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cate smoking as a risk factor for breast cancer, it is still unclear why breast tissue should be resistant to the harmful effects of cigarette smoke. Cigarettes contain roughly 3,600 chemicals, many of which are carcinogens. These include aryl aromatic amines, polycyclic aromatic hydrocarbons, heterocyclic amines and *N*-nitrosamines. Studies of laboratory animals show that many of these chemicals spur cells in the milk ducts to become cancerous; other studies of breast tissue taken from women indicate that human breast tissue responds to the carcinogens in a similar way. We also know that carcinogens from cigarette smoke reach the human breast: breast milk from women smokers contains nicotine and can cause mutations in cells grown in the lab.

Many researchers concluded that if smoking does contribute to breast cancer, it is only a bit player. But we looked at the results of the previous studies from a different standpoint. In 1994 we hypothesized that the estrogen-lowering (and thus anticancer) effects of smoking and the cancer-causing effects of smoking are in a continual tug of war. In some women, the carcinogenic effects of smoking might be more pronounced, whereas for other women the estrogen-lowering effects of smoking might predominate. Accordingly, we set out to discover what dictates how a woman's breast cells respond to cigarette smoke.

The Liver Connection

To understand how cigarette smoke might be carcinogenic in some women but not others, we must first understand the critical role the liver plays in body chemistry. Once cigarette smoke is inhaled into the lungs, toxic substances in the smoke cross over into the bloodstream, where they are taken up into the liver. The liver is equipped with hundreds of enzymes for detoxifying potentially dangerous chemicals, such as those that might be inhaled or eaten. These enzymes break down toxic chemicals so they can be excreted through the kidneys (as urine), by the gastrointestinal tract (as feces), or by the skin (as part of perspiration). People whose detoxifying enzymes act more slowly than those of others end up exposed longer to carcinogens. In such people, the carcinogens have more time to travel throughout the body to reach virtually every cell—including, in women, those that line the milk ducts, where breast cancer originates.

We began our research on the breast cancer–inducing effects of cigarette smoking by examining the gene that prompts the body to make the enzyme *N*-acetyltransferase 2, also called NAT2. This enzyme, which is active mostly in the liver, normally breaks down aromatic amines, such as those found in cigarette smoke. The *NAT2* gene comes in different forms: some encode slow-acting versions of the enzyme, and others encode fast-acting ones. Using genetic tests, we can determine whether someone has a fast-acting form and is therefore what we call a rapid acetylator, or a slow-acting version and is therefore a slow acetylator.

ROUGHLY HALF OF ALL WOMEN ARE PARTICULARLY SENSITIVE TO THE CARCINOGENS FOUND IN CIGARETTE SMOKE AND SO HAVE A HIGHER RISK OF BREAST CANCER.

We focused on NAT2 for two reasons: the enzyme is known to affect how people respond to certain drugs, and it is also thought to determine whether some people develop specific cancers. For instance, in the 1950s and 1960s, several groups of researchers found that some people were more prone than others to developing side effects while taking the antituberculosis drug isoniazid. These researchers found that people who metabolized the drug slowly—slow acetylators—were more likely to develop liver complications than rapid acetylators.

Both the slow- and fast-acting forms of NAT2 have been associated with an increased risk for cancers of various types. A number of studies have shown that slow acetylators have a higher risk for bladder cancer than rapid acetylators, whereas rapid acetylators are more likely to develop colon cancer. NAT2 has different effects on different chemicals, depending on the structure of the chemical. Researchers now think that slow acetylators have more bladder cancers because they cannot detoxify aromatic amines, carcinogens that are known to cause the disease. On the other hand, scientists speculate that rapid acetylators have an increased risk for colon cancer because NAT2 can activate heterocyclic amines, dietary carcinogens that are formed in the cooking of meats.

Whether someone carries a slow- or fast-acting version of NAT2 depends on the genetic make-up of her parents. We know that the frequency of these genetic variants is more common in some races than others. Roughly 55 percent of all Caucasian and Latin-American women (and men) are slow acetylators. African-American women (and men) are slightly less likely to have the trait; roughly 45 percent of them have the slow-acting form. In contrast, only between 10 and 20 percent of Asians have slow-acting NAT2. People who are of Middle Eastern descent have the highest likelihood of being slow acetylators: between 65 and 99 percent of them share the trait.

A Look at Women Smokers

Our evaluation of NAT2 and its role in breast cancer related to smoking, which was reported in the *Journal of the American Medical Association* in 1996, included only Caucasian women. The participants came from a study conducted by our colleagues in the department of social and preventive medicine at the State University of New York at Buffalo. Altogether, we examined the *NAT2* genes of 631 women; 304 of them had breast cancer. About 53 percent of the women we studied had been or currently were smokers. As predicted, roughly half had the slow-acting form of the NAT2 enzyme.

When we analyzed our results, we initially found—as in previous reports—that smoking was not a risk factor for breast cancer. The women who were heavy smokers had the same rates of breast cancer as light or nonsmokers. And we saw similar breast cancer rates among both slow and rapid acetylators. But when we factored both smoking and being a slow acetylator into the equation, we made an important finding: postmenopausal women who had the slow-acting form of NAT2 and smoked more than 15 cigarettes a day were more likely to develop breast cancer than light smokers or nonsmokers who also had slow-acting NAT2. We also found that postmenopausal women who were slow acetylators and began smoking at an early age (age 17 or younger) had the highest risk of breast cancer. These findings indicate that a postmenopausal

woman with a slow-acting form could elevate her risk for developing breast cancer if she smokes, particularly if she begins smoking when young.

We want to emphasize that the link between slow-acting NAT2, smoking and breast cancer was found only in women who have already undergone menopause. We found that postmenopausal women who smoked more than a pack a day and were slow acetylators had roughly four times the risk of developing breast cancer as did nonsmoking postmenopausal women with the slow-acting version of NAT2. But this is the first of many epidemiological studies on the role of NAT2 and breast cancer; other studies will be needed to confirm our findings.

We still don't understand why we saw a higher risk of breast cancer among postmenopausal women smokers than among their premenopausal counterparts. It could be because estrogens play a greater role in some breast cancers, depending on whether a woman is still menstruating. Accordingly, the balance between estrogens and carcinogens might be tipped toward cancer in postmenopausal women. Smoking might also have less of an apparent effect on premenopausal women because many breast cancers among these women are probably caused by other genetic factors that have not yet been identified. The difference between premenopausal and postmenopausal women might also arise because postmenopausal women have smoked for a longer period, so it follows that they have had more opportunities for tobacco to harm them.

Time to Quit

If having a slow-acting form of NAT2 elevates a woman's risk of breast cancer if she smokes, should scientists develop a clinical test for the enzyme to convince women with slow-acting NAT2 that they should never smoke?

We hope that as more women learn that smoking may cause breast cancer, they will stop. Getting the word out is important because the rates of both smoking and smoking-related illness continue to rise among women in the U.S. But a test based on the *NAT2* gene would have little utility in helping women make decisions about their health. It would be foolhardy for a woman to conclude that if she is a rapid acetylator, it is acceptable for her to smoke. Also, because both rapid and slow acetylators are at risk for other types of cancers caused by smoking, knowing your *NAT2* genetic makeup would not assure that you would not develop some type of cancer.

Besides breast cancer, smoking also causes lung cancer [*see box below*], heart disease and emphysema. This means that women have many reasons not to smoke, regardless of whether they are slow or rapid acetylators. In addition, our results suggest that at least for breast cancer the number of cigarettes you smoke a day is a greater risk factor than the total number of years you have smoked. So even if you have smoked for a long time, quitting now can still reduce your risk of breast cancer. SA

PETER G. SHIELDS and CHRISTINE B. AMBROSONE have a long-standing collaboration studying the molecular epidemiology of cancer. Shields is chief of the Molecular Epidemiology Section in the Laboratory of Human Carcinogenesis at the National Cancer Institute. Ambrosone is a research epidemiologist in the Division of Molecular Epidemiology at the Food and Drug Administration's National Center for Toxicological Research in Jefferson, Ark.

Lung Cancer: Why Women's Risks Are Higher

Lung cancer is the most common cause of cancer death among both men and women, accounting for approximately 160,000 lives lost in the U.S. every year. According to American Cancer Society statistics, one in 12 men will develop lung cancer, and one in 19 women will have the disease.

Although fewer women than men die of lung cancer—it kills roughly 95,000 men and 65,000 women annually—women who smoke are in more danger of the disease than male smokers. Evidence suggests that for the same level of smoking, women have twice the risk of developing lung cancer as men do.

Why the difference? We have a few leads. The types of lung cancers that women suffer are frequently different from those seen in men. Women are more likely to suffer adenocarcinomas, whereas men get more squamous cell carcinomas. Both are dangerous lung cancers that are difficult to treat. But the gender discrepancy in lung cancer types suggests to us that a combination of genetics and a differing response to exposure to carcinogens plays a role.

Other clues also suggest a gender gap in the way women and men develop lung cancer. For example, both sexes tend to have different types of mutations in the *p53* gene. This gene normally serves as a brake to prevent uncontrolled cell growth; when it is mutated, cancer can result. Even though men with lung cancer tend to have more mutations in *p53* than women with the disease, women tend to have more of a mutation called a *G*-to-*T* transversion, which is thought to be caused by smoking. This type of mutation results when toxic chemicals damage guanine (*G*), one of the four units that make up DNA. When a cell with such damaged DNA tries to copy its genes before dividing, it can misread the damaged *G* as a thymine (*T*), another letter of the DNA alphabet. This case of mistaken identity can prevent *p53* from functioning normally, allowing a cell to grow out of control.

Several researchers have recently found that the risk of lung cancer from inherited genes also is different for men and women. As a result, women tend to have higher levels of so-called carcinogen adducts in their lungs than men do. These chemical compounds form when cancer-causing agents stick to DNA. Such carcinogen-DNA combinations increase the chances of mutations that can lead to cancer.

Hormonal differences between men and women undoubtedly contribute to the higher risk of lung cancer among female smokers. Women have higher levels of the hormones estrogen and progesterone than men do. Cells in the lung cancers of women are two times more likely than those of men to bear receptors for estrogen and progesterone, hormones that can stimulate tumor growth.

Considering the gender differences in lung cancer biology, it has been difficult to compare the lung cancer risks of men and women smokers. Because fewer women than men smoke on average, they develop lung cancer less frequently. So far studies examining the risks for lung cancer have not been large enough to explore the differences between men and women. But larger studies by us and others are now in progress. Perhaps within the next few years researchers will have a better understanding of the gender differences in lung cancer. We hope that knowledge will lead to better treatments for women—and men. *—P.G.S. and C.B.A.*

Q&A

Heart Disease and Stroke

KAY CHERNUSH

Martha N. Hill, R.N., Ph.D.

Each year since 1984, cardiovascular diseases have killed more women than men in the U.S. Together heart disease and stroke are the number-one cause of death among American women, claiming more than half a million female lives every year. That's more than the next 16 causes of death among U.S. women combined.

Educating women about their risks for cardiovascular diseases is a high priority for ***MARTHA N. HILL, R.N., Ph.D.,*** *current president of the American Heart Association (AHA). Hill is the first nurse and nonphysician to hold that title. She also serves as director of the Center for Nursing Research at Johns Hopkins University School of Nursing, where she is an internationally known researcher studying hypertension and heart disease. In the following interview,* ***KATHLEEN FACKELMANN,*** *special correspondent for SCIENTIFIC AMERICAN, talks to Hill about why so many women are unaware of their risks for heart disease and stroke and what women can do to stay healthy—particularly in their 50s and 60s.*

Q ***The American Heart Association's recent survey suggests that only 8 percent of American women recognize that heart attack and stroke are their greatest health threats. Why do women fail to appreciate the risk these diseases pose to them?***

A I think it's primarily a lack of awareness of what the facts are. They haven't heard it on the news, and they haven't heard it from their physicians. Most women are shocked when they hear that although one out of eight women die of breast cancer, one out of two die of heart disease or stroke. In other words, half of all American women will die of heart disease or stroke. And yet when we asked American women to name their greatest health threat, 61 percent said cancer, particularly breast cancer. Breast cancer is a very serious threat—we don't underestimate that at all. But we think that women should also be aware of their risk of heart disease and stroke—and know how to protect themselves.

Do women's symptoms of heart disease differ from men's?

Research shows that chest pain remains the most common manifestation of coronary artery disease in both men and women. Like men, women experience angina, the chest pain that occurs when the heart's blood supply is inadequate. But women are more likely than men to have other symptoms that are more subtle, such as nausea, abdominal pain or fatigue. Sometimes we see a woman who has the classic chest pain, but when we probe we find that she's been having these other symptoms for a week or two but didn't recognize them as symptoms of heart disease or that her physician didn't recognize them as such.

Previous research has shown that physicians historically have been less likely to order diagnostic tests—such as electrocardiogram (ECG) stress testing—to detect heart disease in their female patients than in their male patients. Is this still true today?

It is somewhat true, but it is not the only explanation for the lack of predictive diagnostic testing for heart disease in women. Women usually have more advanced heart disease—and at older ages—than men, probably because estrogen protects women from developing coronary artery disease until after menopause. But because they're older, women tend to suffer more

For more information, visit the American Heart Association's site for women at http://women.americanheart.org on the World Wide Web.

from complicating conditions, such as diabetes. All of that poses challenges to diagnosing women accurately. And, of course, until recently women weren't included in very many clinical trials. So for a long time physicians really didn't recognize heart disease as a problem for women. But now there's an increase in awareness. An enormous amount of energy and effort is going into educating physicians and other health care providers—as well as women themselves.

What You Can Do

Are there things women can do to ensure that they are diagnosed and treated effectively for heart disease and stroke?

Yes. One thing women can do is to begin to evaluate their own risk factors. Have you had your cholesterol measured? Do you know what your numbers mean? The American Heart Association has set up a free hotline, 888-MY-HEART, for women to call for information on coronary artery disease and stroke. The AHA has also developed a risk-assessment guide so that women can evaluate their own personal risk factors for heart disease [*see box at right*]. Do this assessment as best you can and then go talk to your doctor. Women need to take charge about knowing what their risk factors are and what they should be doing to protect their own health.

Get all the information you can. In some cases, you have to become very assertive. You have to walk into the doctor's office and say, "Hello, how are you, I've got some questions." Don't wait until you're walking out the door, and the doctor's already got his or her mind on the next patient. Bring your agenda forward early in the visit.

How do the female sex hormones, estrogen and progesterone, protect women from heart disease?

We know that they help lower LDL cholesterol, the bad cholesterol, and that they help to raise HDL cholesterol, the good cholesterol. They also appear to help dilate blood vessels. Bigger coronary arteries are less likely to trigger a heart attack. And it appears that estrogen and progesterone have an antioxidant effect on LDLs. Researchers believe that oxidized LDLs help kick off the process of atherosclerosis. So antioxidants may help by countering that artery-clogging tendency. Many studies are now looking at these issues; I think we will know a lot more soon.

Do women have different risk factors for heart disease than men?

The only gender-specific risk factor that women face is the loss of estrogen that they normally experience with aging. It is quite controversial whether menopause itself increases a woman's risk of heart disease. Women start losing estrogen well before menopause. In fact, you see a drop in estrogen in women in their 40s. Perimenopause—the period around menopause—can add up to a decade or more. So estrogen levels drop earlier than the narrow point in time of menopause, when a woman experiences her last menstrual period.

When should women start thinking about heart disease and stroke?

Don't wait until you haven't had a period for two years. It's never too early to start asking what you can do to prevent, delay or minimize your risk of heart disease. As for stroke, women

What Is Your Risk of Heart Disease and Stroke?

Use this quiz to learn where to focus your efforts in reducing your risk of heart disease and stroke.

✓ **Check all the boxes that apply to you.**

Age

☐ You are a woman over 55 years old, or you have passed through menopause or had your ovaries removed.

Family History

☐ Your father or brother had a heart attack before age 55, or your mother or sister had one before age 65.

☐ You have a close blood relative who had a stroke.

Smoking

☐ You smoke, or you live or work every day with people who smoke.

Cholesterol

☐ Your total cholesterol level is 240 mg/dL or higher.

☐ Your HDL ("good") cholesterol level is less than 35 mg/dL.

☐ You don't know your total cholesterol or HDL levels.

Blood Pressure

☐ Your blood pressure is 140/90 or higher, or a medical professional has told you your blood pressure is too high.

☐ You don't know what your blood pressure is.

Physical Activity

☐ You get less than 30 minutes of physical exercise at least three days each week.

Weight

☐ You are 20 pounds or more over your healthy weight.

Diabetes

☐ You have diabetes or take medication to control your blood glucose (sugar) level.

Medical History

☐ You have coronary artery disease or have had a heart attack.

☐ A doctor has told you you have carotid artery disease—in which the major arteries supplying the brain narrow—or you have had a stroke.

☐ You have an abnormal heartbeat.

If you checked two or more boxes, see your doctor for a more complete evaluation of your risks. Then, work with him or her to reduce, control or prevent as many risk factors as you can.

should start thinking about their risk fairly early in life. A third of the strokes occur before the age of 60. And they are devastating. When a 30-year-old woman has a stroke, it's a tragedy because it was preventable.

An Ounce of Prevention

What does research reveal about how to prevent heart disease in women?

Tobacco is the number-one issue. There's been a steady rise in the number of female smokers, and there's a lot of evidence to suggest that many women use tobacco for weight control—not just to be "cool." The weight issue makes it harder to convince females to quit. What they're concerned about is weight gain as they quit. So an important issue for women who are going to quit smoking is exercise. They should make plans to increase their physical activity because they might eat more. Not smoking is the single most important thing you can do to reduce your risk of heart disease. If you already smoke, quit.

The second most important thing is to know your total cholesterol level and blood pressure. If they are elevated, then initiate lifestyle modifications, such as controlling your weight. You can do that by changing both your eating patterns and your amount of physical activity. The third thing you can do is to look at your alcohol intake, which can elevate both blood pressure and triglycerides, fats in the blood that can pose a particular risk of heart disease for women. So moderate or reduce—or, if necessary, eliminate—alcohol consumption.

Doesn't current research indicate that a drink a day can reduce the risk of heart disease?

Moderate alcohol intake has been associated with lower rates of coronary artery disease. But if you're taking in a lot of empty calories as alcohol, it becomes a problem for weight control. The other issue is there is a relation that is not clearly understood between alcohol and high blood pressure. So women who have high triglycerides and hypertension and are struggling with their weight need to be cautious about drinking.

How can women reduce their risk of stroke?

Number one: they should stop smoking. Number two: women need to look at alternative forms of birth control besides the pill. Number three: women should take steps to reduce their blood pressure and their risk of heart disease. People who suffer from heart disease also have a greater risk of suffering a stroke.

Is it ever too late to reduce our risk of heart attacks and stroke?

Not really. Even in nursing homes, among people who have been very, very sedentary, it has been shown that walking reduces weight. That, in turn, can help reduce blood pressure and improve the cholesterol profile, lowering the risk of heart attack and stroke.

Hormone replacement therapy is known to protect postmenopausal women from heart disease. Yet it can also pose other potential problems, including an increased risk of breast cancer. What's a woman to do?

The question of whether to use hormone replacement therapy has to be an individual decision. A woman really needs to sit down and talk with her physician about her own situation. What stage of menopause is she in? What symptoms is she experiencing? What's her family history of heart disease and cancer? And what about osteoporosis? There's very strong evidence concerning the benefits of hormone replacement therapy for preventing osteoporosis. In my family, for example, all the women get osteoporosis. Frankly, that motivates me to take hormone replacement therapy even more than the potential cardiovascular benefits, because I've seen how painful and debilitating osteoporosis can be.

And as new hormone replacement therapies come out, they'll have fewer adverse effects. For many women, that's going to be very important. Because the data show that about a third of women who have a prescription for hormone replacement therapy never fill it, in part because they're afraid of side effects or breast cancer.

Another third start taking it but then stop within two to three months because they gain weight, develop painful, swollen breasts or experience some other side effect. That tells us that each woman has to be involved in the decision-making process in order to be committed.

How important is obesity as a risk factor for heart disease in women?

The obesity issue is getting quite interesting. More studies are being done in different populations, using different methodologies. Some of the results are contradictory. One study may say obesity is a big risk factor. Other studies say people can gain weight, and as long as they are fortunate enough not to develop high blood pressure, high blood cholesterol or diabetes, it isn't so bad. I believe that obesity by itself can pose a problem: it increases the burden on the heart.

What lies ahead?

This is a very exciting time. There's a lot of research on women and heart disease being conducted right now, and there are numerous opportunities for women to participate in research. Women who have an interest might want to call their local academic health center to find out what kinds of studies are going on in their area. There's an old saying: "You see what you look for, and you look for what you know." Now that we know that heart disease is a major health problem for women, more people are looking for it, and they're seeing it. And that means that more women are being treated earlier in the course of the disease and that many more are learning how they can prevent heart disease and stroke. SA

What Do the Cholesterol Numbers Mean?

The most common cholesterol test is for total cholesterol, measured in milligrams per deciliter of blood (mg/dL). But it's also important to know your HDL level—the amount of high-density lipoprotein, or good cholesterol, in your blood.

The American Heart Association (AHA) says healthy women should have less than 200 mg/dL total cholesterol and at least 35 mg/dL of HDL cholesterol. Total cholesterol levels between 200 and 239 mg/dL are considered borderline-high, and those greater than 240 mg/dL are considered high. If your HDL cholesterol levels are too low, you should also have your low-density lipoprotein (LDL), or bad cholesterol, checked—it should be lower than 130 mg/dL.

Some physicians prefer to analyze your cholesterol ratio: your total cholesterol divided by your HDL cholesterol. The optimal ratio for women is 3.5 to 1; anything above 5 to 1 is a health risk. —*K.F.*

What's in Store for the Future

By the turn of the century, approximately 50 million women in the U.S. will be age 50 or older. Inevitably, that will translate into more women with heart attacks, strokes and other cardiovascular diseases. Unfortunately, most of the scientific knowledge about these disorders has been based on studies of middle-aged men.

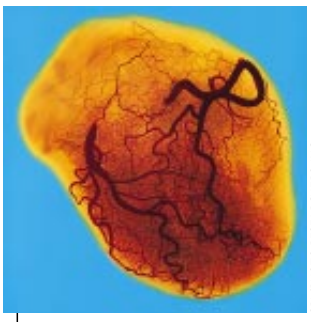
That gender gap will soon narrow. Researchers have launched several studies of cardiovascular disease in women that should yield results in the coming decade. By the time female baby boomers enter the cardiovascular risk zone after menopause, researchers should have a better understanding of the female heart and circulatory system. Here are some of the top questions about women, heart disease and stroke—and how researchers plan to answer them.

Does estrogen really protect against heart disease?

Although many studies have shown a lower rate of heart attacks among women taking estrogen as part of hormone replacement therapy, no single investigation has been large enough or has lasted long enough to prove estrogen's benefits definitively—or to show beyond a doubt that estrogen's heart-healthy effects outweigh its risks for breast cancer.

In 1991 the National Institutes of Health launched a massive clinical trial called the Women's Health Initiative, which will see if estrogen replacement therapy will reduce the risk of heart attack in postmenopausal women. Part of the study will involve more than 25,000 postmenopausal women across the country: some will take estrogen or a combination of estrogen and progestin called hormone replacement therapy; others will take an inactive placebo pill.

Epidemiologist Elizabeth L. Barrett-Connor of the University of California at San Diego predicts that the Women's Health Initiative should answer the estrogen question in five to 10 years. In the meantime, a report published in the *New England Journal of Medicine* last December suggests that an estrogenlike drug named raloxifene lowers women's blood concentrations of low-density lipoprotein (LDL), the bad cholesterol that when elevated leads to atherosclerosis and an increased risk of a heart attack. Raloxifene is one of the new selective estrogen receptor modulators (SERMs), which promise the benefits of estrogen without its cancer risk.



SPL/PHOTO RESEARCHERS, INC.

Heart with coronary arteries injected with dye is seen in a test called an angiogram.

How might estrogen work to protect against heart disease?

If estrogen is confirmed to prevent heart disease, the next question will be how it does so. A preliminary study presented at an American Heart Association conference in March suggests that estrogen shields premenopausal women from heart disease by lowering their blood levels of an enzyme called hepatic lipase. John E. Hokanson of the University of Washington reported at the conference that the hepatic lipase levels of 25 men were 53 percent higher than those of 39 premenopausal women.

Hepatic lipase is known to help form the worst type of LDL—the so-called small, dense LDL—which is most likely to clog arteries. Hokanson notes that estrogen appears to regulate the activity of hepatic lipase. Researchers are now examining whether postmenopausal women, who have lowered estrogen levels, have higher levels of hepatic lipase than premenopausal women.

Should women take aspirin to prevent a heart attack?

Many doctors now tell their healthy male patients to take a low dose of aspirin regularly, based on a report in 1988 by epidemiologist Charles H. Hennekens of Harvard Medical School and his colleagues. The study showed that middle-aged men who took an aspirin every other day cut their risk of suffering a first heart attack dramatically. In 1991 the same researchers published results from the Nurses' Health Study hinting that aspirin's benefits might also transfer to women. After tracking the health of the more than 80,000 women in the Nurses' Health Study for six years, the researchers found that women age 50 and older who took an aspirin between one and six times a week had one-third fewer heart attacks than women who didn't.

Hennekens and his colleagues are now conducting a study to evaluate the risks and benefits of low-dose aspirin versus a placebo among another group of 40,000 female doctors, nurses and other health professionals. Within the next several years, Hennekens says, the new Women's Health Study should indicate whether women would be wise to pop an aspirin every other day along with their male partners.

Do vitamins prevent heart disease in women?

No wonder women are confused. In 1993 the Nurses' Health Study showed that women who took vitamin E supplements regularly had a lower risk of heart disease than women who didn't. But three years later a study by Lawrence H. Kushi of the University of Minnesota School of Public Health indicated that women can get the heart benefits of vitamin E only by eating a diet rich in the nutrient—not by taking dietary supplements.

The Women's Health Study should clear up the confusion over vitamin E within three to four years. It should also confirm the heart benefits of vitamins B_6 and folate, which the Nurses' Health Study earlier this year suggested might also reduce women's risks for heart disease. But even once the results on B_6 and folate are in, Hennekens advises that it is most important for women to focus on reducing their known risk factors for heart disease.

Why are African-American women at greater risk of dying from cardiovascular disease than Caucasian women?

Black women with cardiovascular disease are 69 percent more likely to die than their white counterparts, according to the American Heart Association. To account for this racial disparity, Lori J. Mosca—a preventive cardiologist at the University of Michigan and a member of the American Heart Association's task force on women and cardiovascular disease—and her colleagues are now analyzing health data gathered over the past 40 years on 30,000 white and black women. Mosca speculates that black women are more likely to die than white women because they tend to have more cardiovascular risk factors, such as high blood pressure. Left untreated, high blood pressure can result in more severe heart disease and a greater risk of death, she says. Mosca and her team expect preliminary results by 2000. —*K.F.*

Fat Chances

Given the limited success of dieting—and the risks—is it better just to stay plump?

by Carol Ezzell, *staff writer*

I couldn't believe my eyes. But there it was, printed in an editorial entitled "Losing Weight—An Ill-Fated New Year's Resolution" in the January 1 *New England Journal of Medicine*: "Unfortunately, the data…showing the beneficial effects of weight loss are limited, fragmentary and often ambiguous."

For someone like me who has struggled with her weight for years, this dry pronouncement from the medical profession's equivalent of the Voice on High was nothing short of a revelation. As a chubby child, a "baby-fat" teenager and a Rubenesque woman, nearly all my visits to doctors have inevitably ended with some version of the statement, "If you could lose 10/20/30 pounds, you would sleep better/have more energy/have lower blood pressure/(fill in blank here)."

Lose weight? In theory, it's no problem. I'm an expert at counting calories, calculating fat grams and figuring out just how much time on the StairMaster absolves the sin of eating an Oreo. I'm a veteran of the Grapefruit Diet, Weight Watchers and Diet Center, and I even survived the deadly liquid-protein diets of the 1970s. I took my first diet drug—one of Mother's prescription tablets cut in half—at age 10. I calculate that since the age of 18, I've lost (and gained and lost again) a total of at least 120 pounds—and at 5′6″ I've never weighed more than 196.

The pitfall to losing weight, as every serious dieter knows, is that what comes off doesn't usually stay off. A group of experts convened in 1992 by the National Institutes of Health concluded that at least 90 percent of dieters put the pounds right back on within five years. And losing weight and keeping if off becomes harder and harder as we get older; even thin people tend to gain between 10 and 20 pounds between their 20s and 60s.

So I found myself cheering inwardly when I read the *New England Journal* editorial. Could this mean that it's okay—healthwise, if not socially—to be fat? Should people like me call a truce in their battles with their bodies and just get on with life? Or would we just be deluding ourselves?

A Widening Problem?

There are a lot of us. Indeed, a startling percentage of women in the U.S. fall into the category "obese," including some who might be startled because they probably consider themselves simply plump. The National Center for Health Statistics says that more than one third of all American women are overweight, including nearly half of those between the ages of 55 and 64. The market for women's plus sizes (sizes 16 and up) is a booming $22.7 billion a year.

African-American and Latin-American women are even more likely than Caucasian women to be obese: the Second National Health and Nutrition Examination Survey found that 44 percent of black women and 35 to 40 percent of Hispanic-American women are overweight, compared with 25 percent of white women.

Although socioeconomic factors and cultural differences in diet undoubtedly play a role in the racial breakdown of obesity, most obesity researchers believe genetics is also important. (That is, after all, why they study the genetics of mouse strains with names like Obese and Tubby.) In a telling study reported earlier this year, Claude Bouchard of the University of Laval in Quebec and his colleagues found that both members of 12 pairs of adult male twins who ate 1,000 extra calories a day for 100 days gained the same amount of weight. But the exact amount of weight the men gained varied up to sixfold between sets of twins. Such indications that human obesity has a genetic underpinning don't shock me: both my grandmothers and most of my great-aunts tipped the scales at 250 plus, even though the tallest was 5′5″. (Of course, it could have been the family recipe for that time-honored Southern dish, pecan pie.)

The Risks of Being Fat

Despite the fact that obesity is so prevalent, sound medical advice is hard to come by. It's tough to know whom to believe. When launching the nonprofit organization Shape Up America! in 1994, former Surgeon General C. Everett Koop said obesity causes 300,000 deaths in the U.S. every year, second only to smoking. But in their January editorial, the *New England Journal*'s top editors, Jerome P. Kassirer and Marcia Angell, called the 300,000 figure "by no means well established" and wrote that it is "derived from weak or incomplete data."

So what are healthy figures—both in terms of statistics and body weight? Prompting the editorial was a report published in the same issue of the journal by June Stevens of the Uni-

DAVID HURN *Magnum*

More than one third of U.S. women are overweight. But many women have trouble weighing the risks of carrying extra pounds against the risks of dieting.

versity of North Carolina at Chapel Hill and her colleagues. Stevens and her co-workers reported the results of analyzing health data gathered from 262,019 female and 62,116 male nonsmokers during the American Cancer Society's Cancer Prevention Study I, which was conducted between 1960 and 1972. The researchers found that excess body weight slightly increases the risk of death from any cause among people between 30 and 74 years of age.

The Stevens report was by no means an unusual finding: in 1995 the *New England Journal* published a study linking body weight and mortality in 115,195 women between 30 and 55 years old who were part of the massive, ongoing Nurses' Health Study. And last year the *Journal of the American Medical Association* (*JAMA*) weighed in with two reports on the health hazards of obesity in women. In a separate report in *JAMA* on data from the Nurses' Health Study, a group from Harvard Medical School found that women who put on weight as adults were more likely to develop breast cancer after menopause. And in yet another report, some of the same researchers found that overweight women have an increased risk of stroke. Other studies have linked obesity with gallstones, noninsulin-dependent—or Type II—diabetes and joint degeneration.

But in most of these studies, the relative risk conferred by carrying some extra weight was less than 2.0, which means that fat women were not even twice as likely to die or suffer breast cancer or stroke than their thinner counterparts. In epidemiological terms, this just isn't much.

The Risks of Dieting

So if obesity confers only a modest increase in mortality, what about the risks of striving to be thin? Extreme diets are known to pose health risks by depleting the body of vitamins and nutrients. But what about the new wonder drugs?

They, too, can be dangerous. By now, most people have heard of the demise of the diet-drug combo fen-phen (fenfluramine/phentermine). Fen-phen crashed and burned last September when Wyeth-Ayerst Laboratories took half of the duo—fenfluramine—off the market at the behest of the Food and Drug Administration. The decision followed reports that some women who had taken fenfluramine developed abnormalities in their heart valves, apparently because the drug elevated blood levels of the neurotransmitter serotonin, the same neurochemical boosted in the brain by Prozac. Wyeth-Ayerst also pulled fenfluramine's chemical cousin, dexfenfluramine (Redux), from pharmacy shelves.

In the aftermath of fen-phen, Knoll Pharmaceuticals delayed marketing its new drug sibutramine (Reductil), which increases brain levels of serotonin and another neurotransmitter, noradrenaline. And on March 13, an FDA advisory committee deadlocked over recommending Hoffmann–La Roche's orlistat (also called Xenical), which blocks the enzymes that break down fat in the intestines, allowing fat to pass through the gut undigested. The panel said it was confounded by evidence that the drug might cause or exacerbate breast cancer.

Confusion Reigns

So I'm back to where I was when I first saw the *New England Journal* editorial. Given the current state of affairs, no wonder we're all confused. Depending on your state of mind, you can find enough scary medical evidence to get you back to eating rabbit food or sufficient uncertainty to justify an apologia for staying adipose.

The bottom line is that researchers still don't know why some of us are fatter than others. The interpersonal differences in body fatness can't be explained by food intake, physical activity, genetics or metabolism alone.

Some researchers argue that drugs such as fen-phen, sibutramine and orlistat will never eliminate obesity, because the system of body-weight maintenance is like a balloon: pinch it at one end, and it will compensate by swelling at the other. In the January issue of the *American Journal of Clinical Nutrition*, Jules Hirsch of the Rockefeller University wrote that the mechanisms that determine body weight are carefully balanced. Accordingly, taking a drug to reduce hunger might just cause a reduction in metabolism to save energy, and a drug that ramps up metabolism just might make someone eat more to keep up.

So, is it time to join the National Association to Advance Fat Acceptance? That's up to you. Myself, I draw comfort from a study published in *JAMA* last year by the Cooper Institute for Aerobics Research in Dallas that found that fat people who exercised on a regular basis were less likely to die prematurely than thin people with poor physical fitness. So I'm going to continue to Jazzercise, swing dance and scuba dive—and try to eat moderately and well. I'm not going to take any more diet drugs, but I'm also not going to give up the good fight to be healthy. SA

Are You Obese? (You Might Be Surprised)

It's a loaded word that no one wants pinned to them. Think "obese," and an image like the circus Fat Lady pops into mind. That's right, of course: a consensus statement developed by the National Institutes of Health has defined "extreme obesity" as weighing twice the desirable weight for one's height or being 100 pounds over that desirable weight. But the NIH also indicated that being 20 percent heavier than the desirable weight for your height is considered obese.

Where do you fit? To find out, calculate your body mass index (BMI).

$$\text{Your BMI} = \frac{\text{Your weight in pounds} \times 700}{(\text{Your height in inches})^2}$$

Scientific studies have used a wide range of BMIs—from below 27 to over 30—to define obesity. But most researchers say if you're a woman and your BMI is greater than 27, you're obese. The optimal BMI is generally considered to be 21.

What does someone with a BMI of 27 look like? Emme, the plus-size supermodel and host of *Fashion Emergency* on E! Entertainment Television, wears a size 14 or 16 and weighs 190 pounds at 5'11". That makes her BMI 26.4. —*C.E.*

PHOTOGRAPH BY JAYNE WEXLER; HAIR AND MAKEUP BY LANA GERSMAN; BACKDROPS BY CHARLES BRODERSON

There are 15 million women in the U.S. older than 70. By the year 2030, people over the age of 65 will constitute 20 percent of the total U.S. population.

70s and Up

FACT SHEET

What women in their 70s and up need to know

AARON STRONG *Liaison International*

Medical studies have shown that having pets can lower blood pressure, shorten hospital stays and encourage social interaction among older people. Call your local animal shelter for more information about **adopting a pet.**

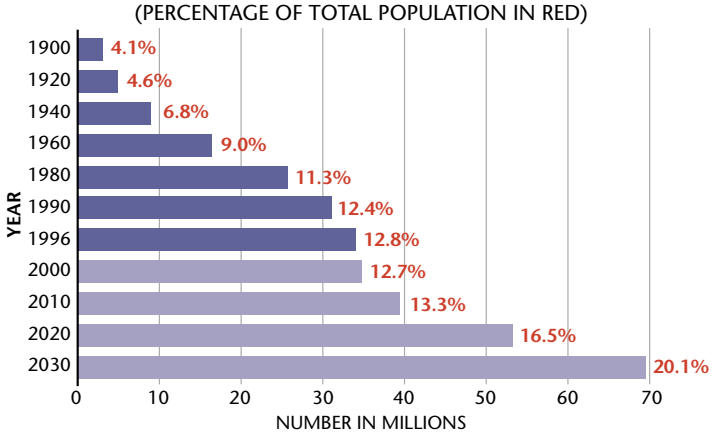
U.S. DEATHS in 1995

from cardiovascular disease:
455,152 men
505,440 women

from cancer (all forms):
281,611 men
256,844 women

Do you know the difference between a nursing home and an **assisted-living facility?** The Department of Health and Human Services operates a directory assistance service to help older people find answers to their questions and locate resources in their community. Call 800-677-1116 or check out http://www.ageinfo.org/elderloc/elderloc.html on the World Wide Web.

NUMBER OF AMERICANS AGED 65 OR OLDER
(PERCENTAGE OF TOTAL POPULATION IN RED)



SOURCE: U.S. Bureau of the Census

Choose one **pharmacy** that you can go to consistently for all your medications. If the pharmacists get to know you, they'll be aware of all the drugs you're taking and may be able to alert you if you begin taking medicines that aren't compatible with one another.

Are you not enjoying retirement? Planning some new activities could make you feel better. But if not, speak up—you may be suffering from depression. Your doctor might be able to help by prescribing antidepressant medication or recommending a psychotherapist.

CHECKUP

Essential medical exams for women in their 70s and up

VACCINATIONS

Every year 50,000 to 70,000 Americans die from diseases that could have been prevented by vaccinations. The Centers for Disease Control and Prevention (CDC) recommends that adults age 65 and older receive vaccinations against tetanus every 10 years, an annual shot against influenza and a vaccine against pneumonia. The Administration on Aging also suggests that people who have blood-clotting disorders or who require kidney dialysis be vaccinated against hepatitis. Vaccinations aren't just for kids—if you have questions, call the CDC at 800-CDC-SHOT.

COST: The cost for each vaccination is different but should be covered by insurance.

EYE EXAM

Although eyes commonly weaken with age, many diseases of the eye can be effectively treated if caught early. The National Eye Institute recommends an eye exam once every two years for everyone older than 60 and once a year if you're diabetic. The eye doctor will test your eyesight and your glasses and should check for glaucoma, cataracts and macular degeneration (the deterioration of the central part of the retina). If you begin to notice changes in your eyesight, the National Institute on Aging suggests adding brighter lights in your home—it may help you see better for reading and other tasks and should help prevent accidents.

COST: $50–$100

DENTAL EXAM

Losing your teeth is not a natural part of aging. Schedule annual dental appointments to keep your teeth healthy. And if you wear dentures, you still need to go in: have your dentures professionally cleaned and adjusted for fit regularly or if your weight changes by more than 10 pounds or so.

COST: $60–$200

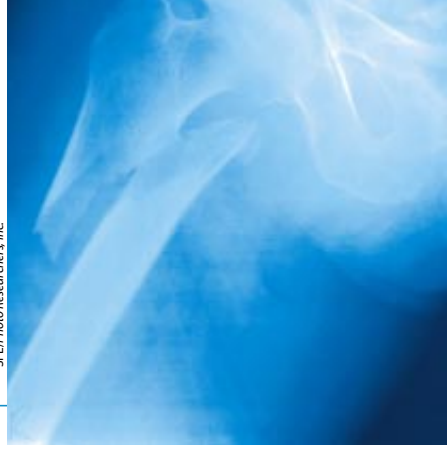
Don't suffer in silence from urinary incontinence. At least one out of 10 people over age 65 in the U.S. suffers occasional lack of bladder control. If you begin to experience problems, see your doctor: incontinence is very often treatable.

Women who smoke have

6% less

bone mass by age 80 than women who don't smoke.

(*British Medical Journal*, October 1997)



SPL/Photo Researchers, Inc.

Are you WEB-savvy?

SeniorNet is a nonprofit organization that offers classes around the country for older Americans who want to learn about computers and the Internet. Call 415-352-1210 to find the center nearest you. Or if you're on-line and want to learn more, visit their site at http://www.seniornet.org/index.html on the World Wide Web.

*For people between 65 and 84 years old, **falls** are the second leading cause of death from injury and the foremost cause for those 85 years and older. **Fractures** occur in 5 percent of all falls; hip fractures are the most serious of injuries and result in the greatest number of deaths.*

HEART DISEASE SCREENING

Doctors rely on a variety of tests to look for heart disease, the leading killer of women (and men) in the U.S. Have your cholesterol and blood pressure checked regularly. If your doctor suspects heart disease, she may refer you for one or several of the following tests: an electrocardiogram (which measures electrical activity of the heart); a stress or treadmill test (which records heartbeat during exercise); nuclear scanning (which can show damaged areas of the heart); or coronary angiography (which examines coronary arteries).

COST: Variable

COLORECTAL CANCER SCREENING

Physical inactivity and older age are two risk factors associated with cancers of the colon and rectum, so continue to schedule regular exams to screen for these diseases. The American Cancer Society (ACS) recommends a few options, including a digital rectal examination, fecal occult blood tests, sigmoidoscopy (inspection of the lower large intestine) and colonoscopy (inspection of the entire large intestine); ask your doctor which is appropriate for you. Symptoms of colorectal cancer may include changes in bowel habits for more than a few days, rectal bleeding and, in some patients, cramping or stomach pain.

COST: Variable; be sure to find out which tests are covered by your insurance.

MAMMOGRAM

According to the National Cancer Institute, one in 14 women will develop breast cancer by age 70; by age 80 the number increases to one in 10. Schedule an annual mammogram—the earlier you detect breast cancer, the better.

COST: $50–$150

SKIN EXAM

Keep up your annual skin examinations to check for skin cancer. In addition, your skin may be more sensitive these days—to sunlight, bruises, sores and dryness. Be aware of exposure to the elements and keep your skin clean and well moisturized.

COST: Included in a routine visit to the doctor.

BONE DENSITY EXAM

Some 20 million American women are affected by osteoporosis. Ask your doctor if you should have a bone density scan, which is an x-ray of your bones that can detect bone loss. Your doctor may recommend hormone therapy or other drugs, diet changes or exercise to increase the mass and strength of your bones. For more information on osteoporosis, call the National Osteoporosis Foundation's Official Action Line at 800-464-6700.

COST: $100–$300. Medicare pays in some states. But beware, not all private insurers will cover this test; ask before you go to the doctor.

PELVIC EXAM AND PAP TEST

Although your risk of developing cervical cancer doesn't increase with age, the risk of ovarian cancer does. Half of all women diagnosed with ovarian cancer are older than 65, according to the ACS, and the pelvic exam is the only way to catch this disease early. The ACS recommends an annual pelvic exam and Pap test to screen for these cancers.

COST: Pelvic exam $40–$100; Pap test $20–$60. Usually covered by insurance.

HEARING TEST

More than one third of all Americans between the ages of 65 and 74 experience some natural hearing loss, but you can get help. If words become hard to understand or if you begin to hear hissing or ringing noises in the background, find an audiologist and have your hearing tested.

The audiologist will measure your ability to hear sounds at different pitches and volumes and may suggest a hearing aid to help amplify the sounds coming into your ear. And because there are different types of hearing loss, there are different types of hearing aids. The American Speech-Language Hearing Association (ASHA) has a guide to choosing hearing aids on the Internet, complete with their descriptions and prices; visit the site at http://www.asha.org/consumers/brochures/hearing_aid.htm on the World Wide Web. Call the ASHA at 800-498-2071 for more information or to find an audiologist in your area.

COST: Hearing test $10–$100

COMPILED BY STEPHANIE J. ARTHUR AND KRISTA MCKINSEY; GRAPH BY LAURIE GRACE

Why Women Live Longer than Men

by Thomas T. Perls, M.D., M.P.H.
Harvard Medical School

Ruth C. Fretts, M.D., M.P.H.
Harvard Medical School

Women around the world have a survival advantage over men—sometimes by as much as 10 years. What gives them the upper hand?

It is a fact of life that men enjoy certain physical advantages over women. On average, men are stronger, taller, faster and less likely to be overweight. But none of these attributes seem to matter over the long haul. For whatever the physical virtues of maleness, longevity is not among them.

Women, as a group, live longer than men. In all developed countries and most undeveloped ones, women outlive men, sometimes by a margin of as much as 10 years. In the U.S., life expectancy at birth is about 79 years for women and about 72 years for men. The gender discrepancy is most pronounced in the very old: among centenarians worldwide, women outnumber men nine to one. The gender gap has widened in this century as gains in female life expectancy have exceeded those for males.

The death rates for women are lower than those for men at all ages—even before birth. Although boys start life with some numerical leverage—about 115 males are conceived for every 100 females—their numbers are preferentially whittled down thereafter. Just 104 boys are born for every 100 girls because of the disproportionate rate of spontaneous abortions, stillbirths and miscarriages of male fetuses. More boys than girls die in infancy. And during each subsequent year of life, mortality rates for males exceed those for females, so that by age 25 women are in the majority.

For us, these statistics raise two questions: Why do men die so young? And why do women die so old? From the outset we would like to admit that we have no definitive answers to these questions. But the available evidence implicates behavioral as well as biological differences between the sexes, differences in the effects of medical technology, as well as social and psychological factors. Ultimately, our investigation of the gender gap in life span has led us to posit an evolutionary explanation, one that suggests that female longevity is more essential, from a Darwinian perspective, than the prolonged survival of males. The good news is that in spite of this evolutionary imperative, the gap between male and female life expectancy may now be narrowing. The bad news is that some of this convergence may be the result of women suffering more from what used to be considered "male" diseases.

Toxic Testosterone

Comparison of the death rates for men and women in the U.S. at various ages reveals gender differences in mortality patterns [*see graph on page 102*]. Although death rates are higher for males than females at all ages, the difference between the sexes is more pronounced at certain stages of life. Between 15 and 24 years, for example, the male-to-female mortality ratio peaks because of a sudden surge in male deaths with the onset of puberty. During this period, men are three times more likely to die than women, and most of the male fatalities are caused by reckless behavior or violence. Motor vehicle accidents are the most common cause of death for males in this age group, followed by homicide, suicide, cancer and drowning. Interestingly, a surge in male mortality has been observed in other primates at a similar stage in life: in young adult male macaques, for example, rates of death and "disappearance" are high compared with those of female macaques.

The difference between male and female mortality declines until late middle age, when the mortality ratio plateaus. In the 55- to 64-year-old age group, behavior-related fatalities are still

J. W. STEWART

Hormones, genetics and the fact that women go through menopause may explain why women live longer than men on average.

among the most common causes of death for men and are still much higher in men than in women. Men of this age are more than twice as likely as women to die in car accidents, for example, and almost four times as likely to take their own lives.

Illnesses related to smoking and alcohol consumption also kill more men than women in this age group. But heart disease is the main cause of the gender gap here. Men experience an exponential rise in the risk of heart disease beginning in their 40s; in contrast, women's risk of dying from heart disease does not begin to increase until after menopause, and it approaches the male risk only in extreme old age. Although the gender gap in this age group is smaller than the one described for young adults, the number of people affected by it is far greater. Whereas accidents claim the lives of 45 of every 100,000 young adult males annually, heart disease—the leading cause of death in men and women alike—kills 500 of every 100,000 men between the ages of 55 and 64 every year.

Experts suspect that gender differences in mortality patterns may be influenced at least in part by sex hormones, namely the male hormone testosterone and the female hormone estrogen. The conspicuous peak in the sex-mortality ratio at puberty, for example, coincides with increased testosterone production in men. Because the male hormone has been linked with aggression and competitiveness as well as libido, some researchers ascribe this spike in male mortality to "testosterone toxicity." Later in life, testosterone puts men at risk biologically as well as behaviorally. It increases blood levels of the bad cholesterol (known as LDL, for low-density lipoprotein) and decreases levels of the good one (HDL, for high-density lipoprotein), putting men at greater risk of heart disease and stroke.

Estrogen, on the other hand, has beneficial effects on cardiovascular health, lowering LDL cholesterol and increasing HDL cholesterol. A recent study at the University of Washington suggests that estrogen may exert these effects by regulating the activity of liver enzymes involved in cholesterol metabolism.

Estrogen is also an antioxidant—that is, it neutralizes certain naturally occurring, highly reactive chemicals, called oxygen radicals, that have been implicated in neural and vascular damage and aging. Emerging evidence suggests that treatment with estrogen after menopause reduces a woman's risk of dying from heart disease and stroke, as well as her risk of dying in general. Estrogen therapy has also been shown in some studies to delay the onset of Alzheimer's disease.

It is important to note that with the exception of this evidence regarding estrogen therapy, the relation between sex hormones and mortality patterns is still speculative. Furthermore, any attempt to explain mortality patterns must include the recognition that these trends are relatively recent. As the graph on the next page shows, the two divergences we have been discussing did not emerge until the middle of the century. Before that time, the sex-mortality ratio was constant across age groups for which data are available. The recent changes can probably be accounted for by two societal factors: improvements in obstetrical care, which have dramatically reduced women's risks of dying in childbirth, and an increased availability of guns and cars, which has contributed to more accidental and violent deaths in young males.

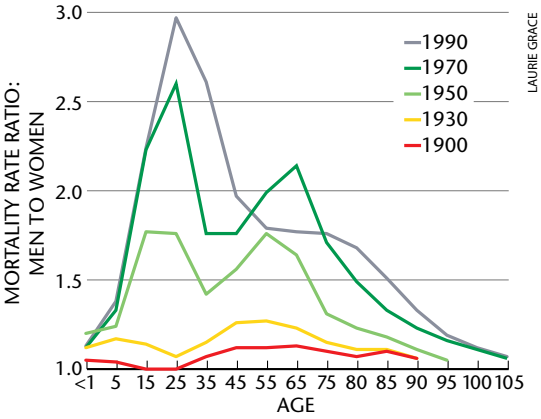
Historical Advantage

Although the reasons women live longer than men may change with time, it seems likely that women have been outliving men for centuries and perhaps longer. Even with the sizable risk conferred by childbirth, women lived longer than men in 1900, and it appears that women have outsurvived men at least since the 1500s, when the first reliable mortality data were kept. Sweden was the first country to collect data on death rates nationally; in that country's earliest records, between 1751 and 1790, the average life expectancy at birth was 36.6 years for women and 33.7 years for men.

Death rates in less developed countries, whose citizens have limited access to cars, guns and maternal care, also provide a measure of mortality before modernity. At present, the only countries in which male life expectancy exceeds that for females are those with long-standing sexual discrimination—including Bangladesh, India and Pakistan—where social pressures and practices such as female infanticide and bride-burning result in unique "losses" of females.

The fact that women live longer than men does not, however, mean that they necessarily enjoy better health. It could be that women live with their diseases, while men die from them. Indeed, there is a difference between the sexes in disease patterns, with women having more chronic nonfatal conditions—such as arthritis, osteoporosis and autoimmune disorders—and men having more fatal conditions, such as heart disease and cancer.

COMPARISON OF DEATH RATES FOR U.S. MEN AND WOMEN



LAURIE GRACE

Differences in the death rates of U.S. men and women have changed over the past century. Mortality has been consistently higher for men than for women at all ages (the male-to-female mortality ratio is more than one). In recent decades, however, this discrepancy has become even more pronounced at certain stages of life.

SOURCE: Social Security Administration

Survival of the Fittest

To understand better the forces that control human aging and longevity, we have tried to determine whether the longer life span of females might be part of some grand Darwinian scheme. Gender differences in longevity have been observed in other members of the animal kingdom: in fact, in almost all species that have been observed in the wild, females tend to live longer than males. Female macaques live an average of eight years longer than males, for example, and female sperm whales outlive their male counterparts by an average of 30 years.

It seems that a species' life span is roughly correlated with the length of time that its young remain dependent on adults. We have come to believe that when a significant, long-term investment of energy is required to ensure the survival of offspring, evolution favors longevity—in particular, female longevity. Indeed, we believe that the necessity for female longevity in the human reproductive cycle has determined the length of the human life span.

We start with the assumption that the longer a woman lives and the more slowly she ages, the more offspring she can produce and rear to adulthood. Long-lived women therefore have a selective advantage over women who die young. Long-lived men would also have an evolutionary advantage over their shorter-lived peers. But primate studies suggest that men's reproductive capacity is actually limited more by their access to females than by life span. Hence, the advantage of longevity for men would not be nearly as significant as it is for women. And because males historically are not as involved in child care as females, in the not so distant evolutionary past the survival of a man's offspring depended not so much on how long he lived as on how long the children's mother lived.

One might think that the existence of menopause halts the transmission of a woman's genes and thus contravenes the evolutionary argument for female longevity. We think just the opposite: menopause confers a selective advantage and promotes longer life by protecting females from the increased mortality risk associated with childbirth at advanced age. Even today this increase in risk is considerable: a woman in her 40s is four to five times more likely to die in childbirth than a 20-year-old.

When menopause evolved, maternal mortality would have been much greater. If offspring require a significant maternal investment of time and energy to survive—which human children most certainly do—then there probably comes a point in a woman's life when it is more efficient to pass on her genes by caring for the children and grandchildren she already has than by producing and nurturing more children, risking death and the death of her existing children in the bargain. The argument that menopause is an evolutionary adaptation was first developed in 1957 by George C. Williams, now at the State University of New York at Stony Brook, and recent anthropological studies have supported it. Because human children are dependent for such a long time, continued health and longevity may enhance older women's contribution to the gene pool even when they can no longer reproduce.

In our own studies of centenarians, we have found that a surprising proportion of women who lived to be 100 or more gave birth in their 40s. One of our subjects had even had a child at the age of 53. We found that, overall, 100-year-old women were four times as likely to have given birth in their 40s as a control group of women, born in the same year, who died at the age of 73. This observation reinforces our suspicion that longevity is linked with fecundity at an advanced age. Of course, we do not mean that having a baby in middle age makes a woman live longer. Rather, it seems that the factors that allow certain older women naturally to conceive and bear children—a slow rate of aging and perhaps also a decreased susceptibility to the diseases associated with aging—also improve these women's chances of living a long time.

We propose that women's longevity edge over men may simply be a by-product of genetic forces that maximized the length of time during which women could bear and raise children and perhaps assist with grandchildren as well. Moreover, male longevity may simply be a function of the fact that men must carry the genes that ensure longevity to pass them on to their daughters. Thus, the necessity of female longevity in the human species may be the force that has determined the natural life span for both men and women.

The Secret to Living Longer

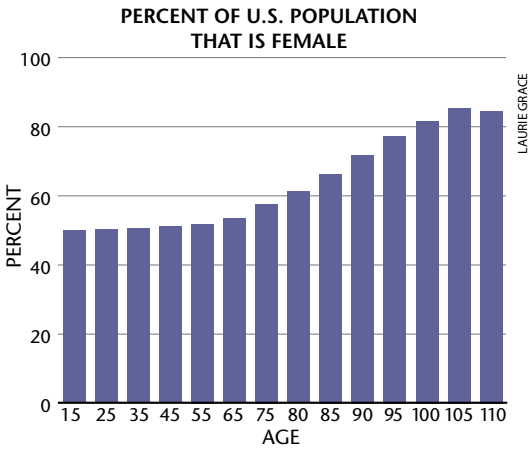
If female longevity is the product of evolutionary forces, then one might wonder what physiological mechanisms have evolved to support the preferential survival of women over men. As we have mentioned, sex hormones are thought to be important factors in determining the relative susceptibilities of the genders to aging and disease. Less obvious is the contribution that menstruation might make to longevity. Because of the monthly shedding of the uterine lining,

premenopausal women typically have 20 percent less blood in their bodies than men and a correspondingly lower iron load. Because iron ions are essential for the formation of oxygen radicals, a lower iron load could lead to a lower rate of aging, cardiovascular disease and other age-related diseases in which oxygen radicals play a role. Indirect support for this theory comes from studies at the University of Kuopio in Finland and the University of Minnesota Medical School. In these studies, male volunteers who made frequent blood donations had less oxidation of LDL cholesterol—a key step in the development of atherosclerosis and heart disease.

Women also have a slower metabolism than men—a distinction that makes them more prone to obesity. But there may also be an inverse relation between metabolic rate and life span. Evidence of this link comes from animal studies of food restriction, which slows metabolic processes: in experiments sponsored by the National Institute on Aging, monkeys that ate 30 percent less of the same diet as their free-feeding peers seemed to age more slowly.

Studies of so-called clock genes in microscopic worms have also demonstrated the connection between metabolic rate and life span. Siegfried Hekimi of McGill University has observed that worms with particular mutations in these genes live five times as long as normal animals and have much slower physiological functions. Although it is still not known why men's metabolism rates are faster than women's, it is becoming clear that this difference is present almost from the moment of conception, when male embryos divide faster than female ones. The faster metabolic rate may make men's cells more vulnerable to breakdown, or it may simply mean that the male life cycle is completed more promptly than the female one.

Finally, chromosomal differences between men and women may also affect their mortality rates. The sex-determining chromosomes can carry genetic mutations that cause a number of life-threatening diseases, including muscular dystrophy and hemophilia. Because women have two X chromosomes, a female with an abnormal gene on one of her X chromosomes can use the normal gene on the other and thereby avoid the expression of disease (although she is still a carrier of the defect). Men, in contrast, have one X chromosome and one Y chromosome, and so they cannot rely on an alternative chromosome if a gene on one of the sex chromosomes is defective.



Women outnumber men by age 25, when they make up 50.3 percent of the U.S. population; by age 100, women comprise 81.7 percent.

SOURCE: Social Security Administration (1990 data)

This disadvantage became more ominous when, in 1985, researchers at Stanford University reported the discovery on the X chromosome of a gene critical to DNA repair. If a man has a defect in this gene, his body's ability to repair the mutations that arise during cell division could be severely compromised. The accumulation of such mutations is thought to contribute to aging and disease.

There is also increasing interest in women's second X chromosome as a longevity factor in and of itself. Although one of the two Xs is randomly inactivated early in life, the second X seems to become more active with increasing age. It may be that genes on the second X "kick in" and compensate for genes on the first X that have been lost or damaged with age. This compensation could have a sizable influence, as it appears that roughly 5 percent of the human genome may reside on the X chromosome. In recent years the X chromosome has also become the focus of the search for genes that might directly determine human life span.

Closing the Gender Gap

Men and women alike have seen profound gains in life expectancy in this century. Since 1900, the average national increase in life expectancy in developed countries has been 71 percent for women and 66 percent for men. This increase cannot be explained by physiological or evolutionary theories. Rather, swift changes in knowledge of health and disease, changes in lifestyle and behavior, and advances in medical technology have greatly improved the chances of both sexes' living to old age.

In the past two decades, however, there has been a notable deceleration in the extension of life expectancy in women. The reasons for this decline are still being debated. Some researchers feel that women in developed countries are close to reaching the natural limits of human life span, and so their gains in life expectancy must inevitably diminish.

But some sociologists have discounted this reasoning, pointing instead to women's changing roles in society. As more women have taken on behaviors and stresses that were formerly confined to men—smoking, drinking and working outside the home—they have become more likely to suffer from diseases that were traditionally considered "masculine." Mortality from lung cancer, for example, has almost tripled in women in the past two decades. Smoking seems to be the "great equalizer" for men and women: current actuarial data from Bragg Associates in Atlanta show that on average middle-aged female smokers live no longer than male smokers do.

In part because of these factors, men's and women's death rates in the U.S. have begun to converge in the past 20 years. But it is primarily the reduction in male mortality, as opposed to the increase in female mortality, that is narrowing this gender gap. In general, the higher a nation's level of social and economic development, the greater the life expectancy for both men and women and the greater the convergence in the two figures.

Research on sex hormones, sex chromosomes and gender-specific behavior is sure to further understanding of the human body well beyond the questions posed by the longevity gender gap. In exploring this intriguing phenomenon, investigators will undoubtedly find clues to how both men and women can live longer and more healthy lives. SA

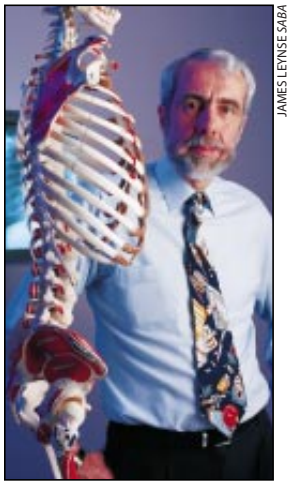
THOMAS T. PERLS and RUTH C. FRETTS share an interest in the association between reproductive issues and longevity. Perls is a geriatrician at Beth Israel Deaconess Medical Center, director of the New England Centenarian Study and an instructor at Harvard Medical School. Fretts is an obstetrician-gynecologist at Beth Israel Deaconess Medical Center and an instructor at Harvard Medical School.

Q&A

Osteoporosis

Donald P. McDonnell, Ph.D.

M. J. SHARP



JAMES LEYNSE *SABA*

Robert Lindsay, M.B.Ch.B., Ph.D.

It's hard to envision a thin, athletic woman as a hip fracture victim waiting to happen. Unfortunately, research shows that women athletes who often diet and don't get enough calcium have among the highest risks for developing osteoporosis when they reach their 50s and 60s. Some young female athletes are also at risk because they lose so much body fat that they stop having their menstrual periods, which lowers their estrogen levels and leads to bone loss. Osteoporosis is characterized by decreased bone mass and an increased risk of broken bones. According to the U.S. National Osteoporosis Foundation, more than 28 million people in the U.S. are at high risk of developing the potentially crippling disorder—and most of them are women. That figure is predicted to jump to 41 million by 2015, when women in the baby boom generation will be beyond menopause.

***KARYN HEDE**, special correspondent for SCIENTIFIC AMERICAN, discusses what women should know about osteoporosis with **DONALD P. McDONNELL, Ph.D.**, associate professor of pharmacology and cancer biology at Duke University Medical Center, and **ROBERT LINDSAY, M.B.Ch.B., Ph.D.**, chief of internal medicine at Helen Hayes Hospital in West Haverstraw, N.Y. McDonnell's research focuses on a new class of compounds called selective estrogen receptor modulators (SERMs), which offer hope for preventing and treating osteoporosis without the side effects of estrogen. Lindsay is founding director of the metabolic bone disease unit at St. Luke's–Roosevelt Hospital in New York City and is the author of over 200 publications on osteoporosis and estrogen replacement therapy.*

Q *What causes osteoporosis? And why are women particularly prone to the disease?*

A McDONNELL: To answer that, I need to describe what usually happens in normal bone. Bones are very complex and dynamic organs. There are basically two types of bone cells: osteoblasts, which make bone, and osteoclasts, which break down bone. Normally, these cells function in concert throughout life to resorb old, worn-out bone and replace it with new bone. In osteoporosis, this balance gets thrown off in favor of the osteoclasts.

The hormone estrogen, which is present in much greater quantities in women than in men, regulates the bone deposition process. A number of sex hormones may be involved in maintaining bone mass. In men, estrogen and androgens are involved. Men have more estrogen than women after menopause, so they are relatively more protected. But men do get osteoporosis, just in lower numbers.

Women have two stages of bone loss: from about age 35 to menopause, and after menopause. We don't really understand the first stage, although estrogen levels have already begun to drop during that time of life. But after menopause, osteoporosis results from the lack of estrogen.

What is known about the role of estrogen in maintaining healthy bones?

McDONNELL: This is a case in which the clinical data have been way ahead of basic science. For years, all we knew was that when you put women on hormone replacement therapy, they stop losing bone and actually regain a small bit of bone mass. But we've had some revealing developments in the laboratory within the past few years. It's becoming clear that estrogen binds to estrogen receptors in bone progenitor cells, the cells that give rise to the osteoblasts and osteoclasts. After menopause, a lack of estrogen actually stimulates production of both cell types—but with a net increase in osteoclasts, which results in a net loss of bone.

LINDSAY: We still do not understand exactly how estrogen controls skeletal remodeling. But when women go through

menopause, the normal bone-remodeling process goes crazy. After the ovaries stop secreting estrogen, the number of sites where the bone cells are breaking down old bone and making new bone increases. Theoretically, the amount of old bone removed should be exactly equal to the amount of new bone laid down. But after menopause there's an imbalance between bone resorption and bone formation in favor of resorption. As a consequence, after each remodeling cycle you end up with slightly less bone.

Who is at risk for developing osteoporosis?

LINDSAY: The major risk factors are age and race: Caucasian and Asian women who have reached menopause have the greatest risk. Having a family history of osteoporosis increases risk because there's a genetic component to the overall amount of bone you start with as an adult. Beyond that, other risk factors are a thin physique, smoking, excessive alcohol consumption and a history of low calcium intake. In addition, some medications, such as steroids, the anticoagulant heparin and anticonvulsants, can accelerate bone loss.

Lowering Your Risk

So what should women with these risk factors do?

LINDSAY: If you have three or more risk factors, you ought to think seriously about having a bone-density scan around the time of menopause. A bone-density scan, technically called dual-energy x-ray absorptiometry (DXA), is used to measure bone mineral density in the spine, hip and wrist, the most common sites for osteoporotic fractures. Bone scans take just a few minutes and result in very low x-ray exposure—about one tenth that of a standard chest x-ray.

Women with low bone density at menopause are very likely to develop fractures; the lower your bone density, the higher your risk. Measurements are based on the mean bone density of a young woman at peak bone mass. Based on the results of the scan, a patient and her physician can decide among several courses of action.

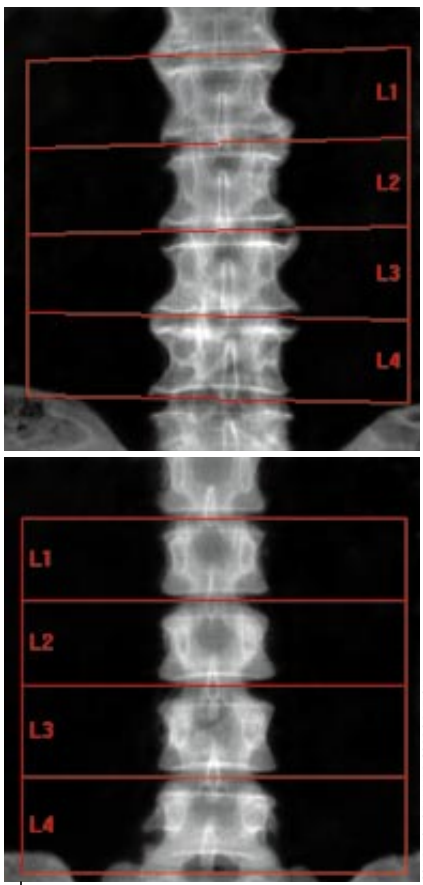
If a woman has high bone density, greater than one standard deviation above normal, her doctor might say, "You don't need to worry; you're not going to get osteoporosis." To a woman with average bone density who is just entering menopause, a physician might say, "We don't know whether you are going to lose bone or not, so come back and get a measurement in two to five years." To get the best reading, that woman should go back and have the measurement done at the same place, on the same machine and preferably with the same technician.

If a woman's bone density is a little lower than average for her age—greater than one standard deviation below normal—and she's 55 years old, her doctor might say, "Here are things you can do to change your lifestyle: stop smoking, reduce your alcohol intake, increase your calcium intake and increase your physical activity." Moderate physical activity not only helps bones grow stronger, it also reduces the risk of falling and breaking a bone better than anything else. That woman's physician would also want to measure her bone density again in a couple of years to see whether she was losing bone rapidly.

A woman with bone density lower than 2.5 standard deviations below normal is at particularly high risk for a fracture and should consider pharmacological intervention.

How accurate is bone-density scanning in predicting a woman's future risk of a bone fracture?

LINDSAY: Bone density is a better predictor of fracture than cholesterol is for heart attack or blood pressure is for stroke. Roughly speaking, a 10 percent reduction in bone density doubles a woman's risk of fracture after menopause.



COURTESY OF LUNAR CORPORATION

A bone scan of the lower spine of a 68-year-old woman with osteoporosis (top) *looks less opaque than a similar scan of the spine of a 52-year-old woman without the disease* (bottom). *The osteoporotic woman's spine is slightly crooked, as indicated by the red lines between the vertebrae. It also bears two abnormal bony growths called osteophytes at the right side of lumbar vertebrae L2 and L3.*

Should premenopausal women have their bone density checked?

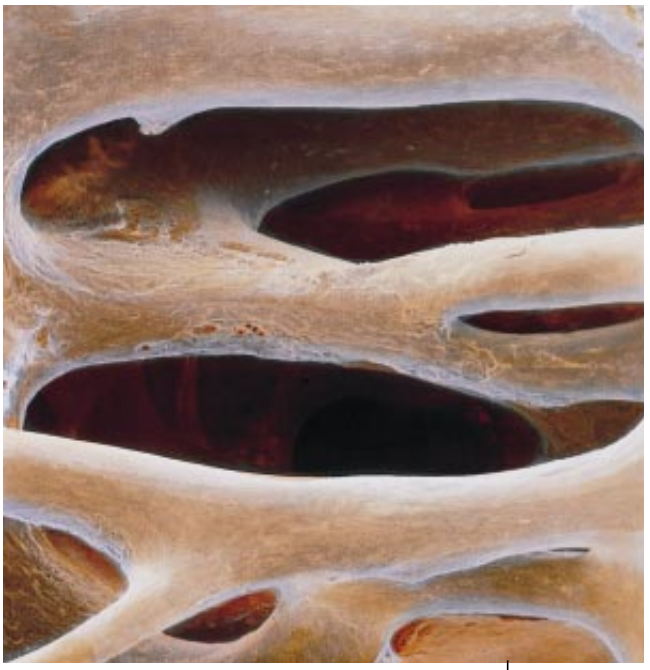
LINDSAY: By and large, premenopausal women don't need to have a bone-density measurement unless they have very clear risk factors for osteoporosis, such as anorexia and problems with the function of their hypothalamus, a region of the brain that's involved with hormone regulation. The time for women to consider a bone scan is somewhere around the perimenopausal years, from the early 40s to the early 50s.

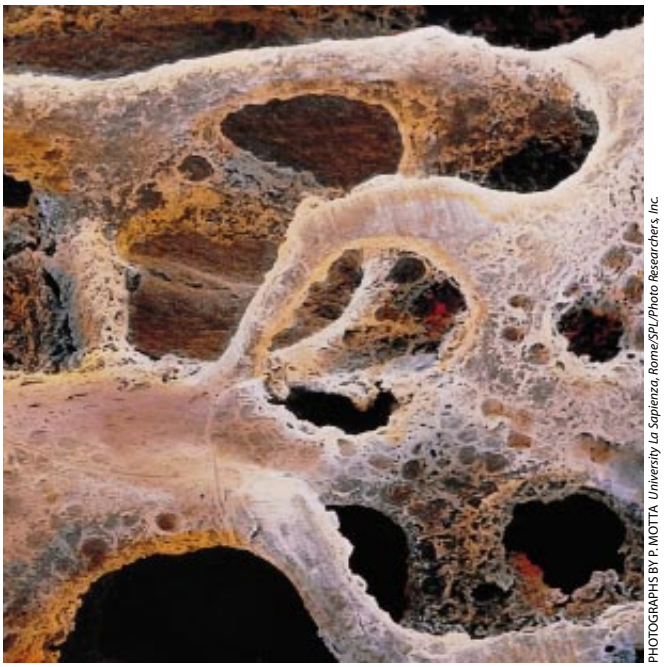
What can premenopausal women do to reduce their future risk of osteoporosis?

LINDSAY: The key to preventing osteoporosis—and many other diseases of aging—is a healthy way of life, particularly a good diet high in calcium. In general, nonpregnant women should take in between 1,000 and 1,500 milligrams of calcium per day, whether in food or as a dietary supplement. The National Health and Nutrition Examination Studies found that the average calcium intake in the U.S. is only about 600 milligrams a day.

The elderly who are homebound or have chronic illnesses must also ensure that they get enough vitamin D, which helps the body use calcium. Most multivitamins contain vitamin D; intake should be five to 7.5 micrograms a day.

Being physically active is also important. Having regular periods is crucial because young women who don't menstruate usually have low estrogen levels, which can mean losing bone mass. And here's yet another reason why a woman should stop smoking: it's as bad for your bones as it is for your lungs and heart.





PHOTOGRAPHS BY P. MOTTA *University La Sapienza, Rome/SPL/Photo Researchers, Inc.*

Healthy bone (left) *appears smooth and sturdy when viewed under the microscope. In contrast, bone from someone who has osteoporosis* (right) *is porous and fragile, making it more susceptible to fracture.*

Treating Osteoporosis

Estrogen is frequently prescribed for menopausal and postmenopausal women to prevent osteoporosis. Yet the use of estrogen has been associated with an increased risk for breast cancer and cancer of the endometrium, the lining of the uterus. Is estrogen still the best treatment for osteoporosis?

McDONNELL: Estrogen has been on the market now for 50 years, and it has an excellent record not only in treating osteoporosis but also in reducing a woman's risk of cardiovascular disease. It also reduces other unwanted side effects of menopause, such as hot flashes. There is a small increase, however, in the incidence of breast cancer among women who take estrogen, although new evidence suggests that women who take estrogen have a lower overall mortality rate. So on balance, the beneficial effects of estrogen for most women greatly outweigh its potential risks. Estrogen with progestin, in a combination called hormone replacement therapy, reduces the risk of endometrial cancer. Still, the breast cancer issue remains at the front of women's minds.

LINDSAY: The gold standard for treatment of osteoporosis is hormone replacement therapy. If women are already on hormones for other reasons—to control menopausal symptoms or because they are concerned about heart disease—then they need do nothing more. Hormone replacement therapy is the first-line therapy for osteoporosis because it has proved to be the best protection against bone loss.

Are there other drugs that can protect against bone loss, without estrogen's side effects?

McDONNELL: One of the newest therapies is a class of drugs called the bisphosphonates, of which the best known is alendronate, or Fosamax. The bisphosphonates do not work like hormones. They do not bind to the estrogen receptor in bone progenitor cells; they enter the bone directly. One hypothesis is that the bisphosphonates reduce the activity of osteoclasts, thereby reducing bone resorption. These agents are very effective in the treatment of osteoporosis. But every drug has a positive side and a negative side. The negative side is that these agents have no beneficial effect on the cardiovascular system and that they do not reduce the other symptoms of menopause, such as hot flashes.

LINDSAY: The people who are most likely to use a bisphosphonate drug such as Fosamax are those who have the highest risk of developing osteoporosis. The problem with Fosamax is that at the higher dose used for treatment, 10 milligrams, it has been associated with some upper gastrointestinal symptoms—heartburn and dyspepsia. That's why it's a second-line therapy for most people. And in rare instances, Fosamax can cause esophageal ulcers.

A new drug called Evista was approved by the Food and Drug Administration last December for treating osteoporosis. How does it work?

McDONNELL: Evista, or raloxifene, is the first approved selective estrogen receptor modulator, or SERM. Other SERMs are now being tested in clinical trials. These drugs function as estrogens in the bone but not in the other organs. In fact, Evista functions as an antiestrogen in the breast by blocking the estrogen receptor, which can spur breast cancer growth. So although it remains to be proved, SERMs might actually reduce a woman's risk of breast cancer. Several small studies have shown that SERMs decrease breast cancer by 70 percent. They can also reduce the risk of endometrial cancer. Long-term studies are still needed to see if that holds up over the long run.

The SERMs have also introduced totally new issues for women to consider. Evista is only about one half to one third as effective as estrogen in preventing bone loss, and the preliminary data suggest that it doesn't begin to match up to estrogen

in protecting against cardiovascular disease. But new SERMs are in development that are likely to show more promise in this regard. Another downside is that current SERMs not only don't protect against hot flashes, they actually induce hot flashes—the reason most menopausal women go to their doctors in the first place. On top of all that is the question of how SERMs will affect the estrogen receptors in the nervous system: Will SERMs decrease cognitive function or increase the risk of Alzheimer's disease? Those are going to be important issues.

How can SERMs act selectively in some tissues but not in others?

McDONNELL: When estrogen binds to its receptors in cells, it activates them by converting them from a square shape into a circular shape. The circular shape is then able to complete all the effects of estrogen in the cell, including turning on some genes. What SERMs do is warp the receptors into new and different shapes. We found that different cells have different abilities to recognize these shapes. For instance, cells in the breast can recognize only a circle. But bone cells aren't that choosy. They can recognize either the circular shape or an alternative shape. So compounds like SERMs that can mold estrogen receptors into another shape can activate the receptors in the bones but can also block the receptors in the breast and endometrium. Using this approach, I believe we will eventually be able to "dial in" certain properties of estrogen, such as protection against heart disease, and "dial out" others, such as its ability to contribute to breast cancer and endometrial cancer.

Taking into consideration the pros and cons of SERMs, who should take them?

McDONNELL: I think SERMs are going to appeal to women who are skeptical of hormone replacement therapy because of the side effects or who have a family history of breast cancer. SERMs might be effective as chemopreventatives against breast cancer and endometrial cancer. Perhaps most important, these new drugs are going to increase women's overall awareness of hormone replacement therapy. When women have more options, they will have more incentive to seek some type of therapy during and after menopause.

The hormone calcitonin is sometimes offered to women as a treatment for osteoporosis. What is calcitonin?

LINDSAY: Calcitonin is normally produced by the thyroid gland to help the body maintain appropriate concentrations of calcium. It is given either as a subcutaneous injection or as a nasal spray, because it is a protein and would be broken down in the stomach if taken by mouth. Before SERMs, calcitonin was the third-line choice for the treatment of osteoporosis because it is not as potent as either alendronate or hormone replacement therapy. Its major advantages are that it is safe and the side effects are modest: some nasal irritation and flushing of the face in the first few weeks of use. It's been around for a long time, and there are no major side effects associated with it. It's used mainly for those who can't or won't take hormones and who can't take alendronate because of gastrointestinal complaints.

If some people have a genetic predisposition to osteoporosis, what will it mean for women if a gene for osteoporosis is found?

LINDSAY: The genetics of osteoporosis is a fascinating field that is growing rapidly. The major approach has been to look for candidate genes and then to evaluate whether different forms of those genes are associated with differences in bone density or the risk of a fracture. The genes that have been looked at include the genes for collagen, which makes up cartilage; the vitamin D receptor; and the estrogen receptor and various growth factors. The very fact that there are all these candidate genes suggests that there may be no single gene that will be useful in a clinical test for osteoporosis risk. Some of the genes are seen more frequently in people who develop fractures, but generally they confer only modest differences in risk.

Another approach has been to look at osteoporosis that runs in families to see if you can identify a common gene in those families. Very little has come out of that work thus far.

I think a genetic test would be of considerable value in terms of guiding lifestyle. We know that lifestyle during the time of young adult life is responsible for about 10 to 20 percent of the variability in bone mass. If we knew there was a gene that had a high prevalence in a family with osteoporosis, physicians could encourage women in such families to build as much bone as possible while they are young through a healthy way of life and getting plenty of calcium.

On the Horizon

What are the most promising therapies coming in the next five years?

McDONNELL: In my mind, we're going toward what I call designer therapies. A woman may go to her doctor and have a family history of osteoporosis but no problems with cardiovascular function. A SERM might be fine for her because she gets protection against bone loss, in the organ where she is most at risk. She's not overtreated. Women themselves are going to decide the market. A woman might say to herself, "SERMs produce hot flashes, so I'll take estrogen for a few years and then switch over to Evista." Women want choices; they want to be much more involved in the treatment of their own menopause.

LINDSAY: I think the most interesting work is being done with agents that might repair the skeleton. Researchers first noted in 1929 that parathyroid hormone can add bone to the skeleton. But that finding was basically ignored until the 1970s, when parathyroid hormone was first synthesized in the lab. Now the first controlled clinical trials of parathyroid hormone as a treatment for osteoporosis have appeared. Last August we published a paper in the journal *Lancet* outlining the results of a three-year study of this hormone. We found that it produces a dramatic increase in bone density—much larger than you see with any of the current therapeutic options. It also appears to reduce the number of spinal fractures. So parathyroid hormone or an analogue might be developed for the treatment of osteoporosis.

I think there's a very rosy outlook for osteoporosis. We have the mechanisms now for diagnosing it, we have some treatment options, and over the next few years we can expect more and better treatments. With all of this, the disease ought to disappear in the next millennium. SA

For more information, visit the National Osteoporosis Foundation at http://www.nof.org on the World Wide Web or call them at 202-223-2226. The association also offers a series of patient education brochures, including one entitled "Osteoporosis: A Woman's Guide."

PHOTOGRAPHS BY ILLANA REIN

At More Risk for Alzheimer's?

Scientists are studying how genes and gender interact in Alzheimer's disease

by Zaven S. Khachaturian, Ph.D.
Ronald & Nancy Reagan Research Institute, Alzheimer's Association

Now and again we all forget where we left our glasses or what we hurried into the kitchen to retrieve. As we get older, these events seem to increase in frequency. But Alzheimer's disease is more than mere forgetfulness. It is a degenerative disease of the brain that causes cognitive dysfunction, behavioral changes and dementia.

The disease, which affects an estimated four million Americans, eventually robs its victims of their memories and their ability to reason. And Alzheimer's appears to affect women more frequently than men.

The finding that women might have an increased susceptibility, particularly women with a certain genetic background, has begun to provide crucial clues about the underlying biology of the disease and new insight into its prevention and treatment. Further, a number of small clinical and epidemiological studies have shown that estrogen replacement therapy appears to help protect postmenopausal women from Alzheimer's. By exploring how estrogen affects the development and activity of the brain, researchers may uncover new ways to protect people at risk for developing Alzheimer's disease.

Since the turn of this century, life expectancy has been steadily increasing. By 2030, some nine million Americans will be 85 or older. Unfortunately, as a greater proportion of the population survives past 85, the number of people with Alzheimer's disease will rise. The prevalence of the disease increases dramatically after age 65, rising from 4 to 6 percent at 65 to 15 to 20 percent at 75 and 30 to 40 percent at 85.

This century has seen dramatic increases in the life expectancy of women compared with that of men. With an elevation of women's social status and the elimination of many of the risks of pregnancy, women are surviving as many as three to 10 years longer than men. Because women are living longer, they are at greater risk for developing Alzheimer's disease—a situation that is reflected in the higher prevalence rates in women.

Yet studies examining the incidence of Alzheimer's—how many people are diagnosed a year—offer conflicting results. Some show higher rates for women; others find no difference. Researchers think the disparity in these incidence studies might reflect the fact that the disease is caused by multiple genes interacting with different environmental influences.

The major risk factors associated with Alzheimer's disease include age, genetic predisposition and gender. But the idea that gender on its own may increase a person's risk is still controversial. A few preliminary studies suggest, however, that gender may interact with one's genetic predisposition

Remembering: Looking at old family photographs stimulates memories for those in the early stages of Alzheimer's disease. A retired psychotherapist, Sarita Stein, 86, stopped seeing patients when she realized she could not remember everything they had told her the previous week.

Coping: Elizabeth Mudd, 71, who runs a small bed-and-breakfast in her home, uses a whiteboard to jog her memory and carries everywhere a small book—full of lists, names, appointments.

somehow to influence the age of onset of the disease. In cases of familial Alzheimer's disease, women are at a higher risk than men of the same age. And they appear to experience an earlier onset. These results suggest that gender may be a risk factor in familial cases of Alzheimer's, and gender may influence the course of the disease, especially in the presence of certain genes.

Over the past few years, researchers have found that mutations or different forms of a particular gene may occur more frequently in people with Alzheimer's than in the general population. In 1992 Alan D. Roses and his collaborators at Duke University found such a relation between one form of the gene for apolipoprotein E (ApoE) on chromosome 19 and an increased risk for late-onset Alzheimer's. This finding established the *APOE* gene as a susceptibility gene for the disease.

The *APOE* gene comes in three varieties, called *APOE2*, *APOE3* and *APOE4*. Roses and his colleagues demonstrated a relation between the average age of onset and the number of *APOE4* copies a person inherits. People who have two copies of *APOE4* tend to get Alzheimer's at an earlier age—sometimes 20 years earlier—than those who have no copies.

But Haydeh Payami and her associates at the Oregon Health Sciences University recently found that the effect of inheriting one copy of *APOE4* differs depending on gender. For men, individuals with two copies of *APOE4* were at the highest risk for developing Alzheimer's, and men possessing one copy, or no copies, had a lower risk. But for women, having one copy of *APOE4* appears to be as bad as having two copies—both genetic situations cause an earlier onset of the disease. If scientists can learn how *APOE4* affects the age of onset, or how gender influences that mechanism, they may be closer to developing interventions that can delay the disease.

Sex and the Brain

Alzheimer's disease is characterized by a progressive decline in memory, orientation, language and communication skills, and the ability to reason. The destruction of critical brain regions starts 20 to 40 years before symptoms are clinically detectable. Ultimately, the disease leads to the loss of increasing numbers of neurons, especially in the hippocampus and cortex—parts of the brain that help to code memories and process information. As increasing numbers of cells in these critical brain regions die, short-term memory fails, and the ability to do familiar tasks begins to decline.

In the late 1970s Barbara B. Sherwin, now at McGill University, first linked a loss of estrogen with memory problems in a group of women who had had their ovaries removed. At the time, few people recognized that estrogen—the hormone that activates and regulates the female reproductive system—may have a number of effects in the human brain, quite apart from its role in reproduction. Then, in the mid-1980s, Howard M. Fillet of the Mount Sinai School of Medicine conducted the first study on the effects of estrogen on cognition in humans. He found that after six weeks of estrogen treatment, three of seven women with Alzheimer's showed significant improvement in attention, orientation, mood and social interactions.

In addition to such prospective investigations exploring estrogen's effects, several groups of researchers were conducting retrospective analyses on previous estrogen studies. In the early 1990s Victor Henderson, Annlia Paganini-Hill and their co-workers at the University of Southern California were among the first to report epidemiological evidence suggesting that estrogen may reduce the risk for Alzheimer's disease. In a larger study conducted in 1996, Henderson and his colleagues analyzed data from a population of nearly 9,000 older women. In studying a subset of about 250 women who had died with Alzheimer's disease, the researchers found that the risk for developing Alzheimer's decreased significantly among women who had received estrogen replacement therapy (ERT). And the women who received the highest doses over the longest times were the most protected.

Other epidemiological studies have provided further confirmation of the protective effects of ERT. Richard Mayeux and his collaborators at Columbia University studied 1,124 older women who were free of the clinical symptoms of Alzheimer's. The researchers found that the age of onset for Alzheimer's was significantly delayed in estrogen users compared with nonusers, and the relative risk was significantly reduced. Women who were on ERT for longer than one year had the greatest risk reduction. None of the 23 women who were taking estrogen when they enrolled in the

study had developed Alzheimer's by the time the paper was published.

And as part of the ongoing Baltimore Longitudinal Study of Aging, conducted by the National Institute on Aging, Claudia H. Kawas and her colleagues at Johns Hopkins University have studied 472 women whose health status has been followed for 16 years. They found that women who take estrogen after menopause reduced their risk of developing Alzheimer's disease by 54 percent.

The Estrogen Link

Animal studies are continuing to reveal how estrogen may enhance brain function. Such findings reinforce the results seen in human clinical studies. It appears that estrogen can improve learning and memory by helping to build and maintain the synapses that connect neurons in the brain.

In the 1970s Bruce S. McEwen and his colleagues at the Rockefeller University first reported that estrogen might have a direct effect on the brains of rats. They had found that estrogen boosts the ability of neurons to relay chemical messages by increasing the levels of acetylcholine, a neurotransmitter involved in learning and memory.

A few years later McEwen, Catherine S. Woolley, Elizabeth Gould and their colleagues discovered that estrogen may enhance learning and memory in animals by helping to build and maintain the synapses through which neurons communicate with one another. Synapses are destroyed in the brains of people with Alzheimer's disease, a loss that hampers their ability to learn and remember information. By removing the ovaries from adult female rats, the Rockefeller researchers found that estrogen deprivation causes a loss of synapses in the hippocampus. Treating these rats with estrogen restored their synapses to normal numbers. Perhaps something similar happens in the brains of postmenopausal women who receive ERT.

Another pioneer in this area was Dominique Toran-Allerand of Columbia University. She showed that in developing neurons grown in a culture dish, estrogen stimulates the growth of axons and dendrites, the neuronal structures that form the synaptic connections.

As we learn more about estrogen, we are finding that it can act alone as an important biological signal. But, more significantly, estrogen also appears to work in a cooperative manner with other classes of signaling molecules to stimulate neuronal growth and activity. Toran-Allerand recently reported that in neurons grown in culture, estrogen increases the production of receptors that bind to nerve growth factor, a hormone necessary for neuronal development and activity. The results suggest that estrogen and nerve growth factor may work together to enhance each other's biological activities.

Caretaking: Dorinda Lord cares for Ethel Burns, 87, round-the-clock, helping this former owner of several dress shops maintain her appearance and interest in fashion.

It is becoming abundantly clear that estrogen has many facets. It plays a key role in growth and repair of neurons in the brain. But it also may help protect nerve cells against damage from free radicals and other cellular toxins. James W. Simpkins and his co-workers at the University of Florida have found that estrogen can directly prevent brain cells from being killed by toxins through an unknown mechanism that does not involve either estrogen receptors or nerve growth factor. Other investigators, including Judes Poirier of McGill University, are studying how ApoE, a cholesterol-transporting protein, may affect the regeneration and repair of neurons. Such animal studies are beginning to suggest how estrogen may protect the brain from destruction by Alzheimer's disease.

ERT or No ERT?

Estrogen replacement therapy might not be the answer for everyone. Fortunately, several studies currently under way should help women to make better-informed decisions about ERT as it relates to Alzheimer's and other diseases. One such study—a part of the Women's Health Initiative of the National Institutes of Health—is monitoring the health of 25,000 women, some of whom are receiving ERT plus progestin, which appears to reduce estrogen's cancer risks. In a few years, the study should provide a clear picture of how ERT is altering the course of Alzheimer's. A second clinical study, headed by Ruth A. Mulnard of the University of California at Irvine, is examining the effects of ERT on 120 women with Alzheimer's disease. The results of this study—sponsored by the National Institute on Aging—should be available within a year.

Toran-Allerand adds a note of caution about interpreting the results of these studies. Many, including the NIH's Women's Health Initiative, involve the use of Premarin, an estrogen preparation made by Wyeth-Ayerst using the urine of pregnant mares. In the future, additional studies comparing different forms of estrogen may lead to the development of therapies that are more effective and have fewer side effects.

As we learn more about estrogen and how it enhances the viability of neurons, we hope to be able to exploit this information to develop better treatments for delaying, and perhaps preventing, this devastating disease. SA

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For more information, contact the Alzheimer's Association at 800-272-3900 or at http://www.alz.org on the World Wide Web. Other Web sites are the National Institute on Aging (NIA) at http://www.nih.gov/nia and the National Institute of Mental Health at http://www.nimh.nih.gov To order "Alzheimer's Disease: Unraveling the Mystery," call the NIA's Alzheimer's Disease Education and Referral Center at 800-438-4380.

Q&A Urinary Incontinence


McNEES AND ASSOCIATES/PHOTOGRAPHY

Rodney A. Appell, M.D.

Millions of women suffer in silence from incontinence—yet experts say the vast majority of them can be helped with proper treatment. ***RODNEY A. APPELL, M.D.,*** *a specialist in urinary incontinence in women at the Cleveland Clinic and a member of the board of directors of the National Association for Continence, talks with* ***MIA SCHMIEDESKAMP,*** *special correspondent for* SCIENTIFIC AMERICAN.

Q *How does urinary incontinence affect women?*

A Women tend to be most susceptible to two types of urinary incontinence. The classic onset of one type, stress incontinence, is the loss of a little urine with a cough or a sneeze; as the condition progresses, any movement that increases pressure in the abdomen—such as bending over—may cause leakage. With so-called urge incontinence, on the other hand, sufferers feel a sudden, urgent need to urinate but can't make it to the bathroom in time. Rarer in women (but quite common in men) is overflow incontinence, in which the bladder empties only partially on demand; urine eventually accumulates in the bladder to the point of spilling out.

Perhaps 20 million people in the U.S. are incontinent; easily 15 to 18 million of these are women. There is a gradual increase in incidence with age: we see more problems in postmenopausal women than in premenopausal women—and urinary incontinence is the second leading cause of admission to nursing homes (after Alzheimer's disease). But this does not mean that a 24-year-old can't be incontinent. No one should be left with the feeling that this is just an old person's problem.

While incontinence is not a life-or-death issue, nothing is more of a quality-of-life issue. Incontinent women give up activities they enjoy and curtail their social lives. And in the most severe cases, incontinence can cause secondary health problems, including recurrent urinary tract infections and breakdown of the skin. To solve this problem, we have to treat the underlying disorder—we've got to get the patient dry.

What causes stress incontinence?

Childbirth seems to be a major cause of stress incontinence in women. Delicate nerves become stretched and injured during labor and delivery, leaving women with poor control of their pelvic muscles. With time, the muscles themselves atrophy, further reducing structural support for the bladder and urethra. Without this support, the urinary tract becomes distorted, and the urethral sphincter—which controls exit of urine from the bladder—weakens, resulting in leakage.

This situation worsens if the fibrous tissues that keep the organs in place are also damaged. The result may be what doctors call prolapse: a shift in the position of the bladder and other organs that further distorts a woman's internal anatomy. Prolapse is especially common in women who have had hysterectomies—removal of the uterus leaves an empty space in which organs can move about more easily.

Menopause is another factor in stress incontinence. The falling levels of estrogen associated with menopause lead to thinning of the tissues of the lower urinary tract, as well as a reduction in the number of receptors in muscle that receive signals from nerve endings. Thus, the effects of childbirth and menopause are additive: pelvic nerves already functioning poorly because of trauma during childbirth may control muscles that are less responsive because of a lack of receptors; the result is muscles that just don't contract as well as before.

What are some causes of urge incontinence?

Urge incontinence is essentially a hyperactivity of the bladder. We know that aging in general plays a role in this disorder, stemming from effects on the central nervous system. With age come reductions of blood flow in the brain; these reductions can impair the brain's function—including its ability to inhibit the activity of the urinary tract. The result is loss of bladder control. And we know that the hormonal changes of menopause further exacerbate this condition.

Stroke is an extreme example of impaired blood flow in the brain; it often leaves its victims severely incontinent. Other diseases, including many neurological disorders—multiple sclerosis and Parkinson's disease, for example—may also result in various types of incontinence. Spinal cord injury or injury to the bladder or urethra can also cause incontinence, as do certain tumors and metabolic diseases. Diabetes is often a factor in overflow incontinence in women.

Are some cases of incontinence transient?

Various diseases and drugs can cause incontinence as a passing symptom or side effect; often these are the first causes we try to rule out when treating patients. For example, urge incontinence is a common symptom of urinary tract infections—a symptom that disappears when we treat the underlying condition.

Some medications used to treat high blood pressure reduce muscle tone in the urethral sphincter, causing stress incontinence; other common culprits include muscle relaxants and drugs on the market for depression, including Prozac and Zoloft. This side effect doesn't occur in everyone, so patients need to tell their doctors if they experience problems. In many cases, other drugs can be substituted that don't cause incontinence.

Other cases of involuntary urine loss are not true incontinence at all. We find this especially in nursing homes, where there are frequently numerous barriers to using the toilet—especially for the bedridden. These patients simply face so many delays in getting to the bathroom that they are often forced to wet themselves. Many of these patients are treated as incontinent and catheterized, when in fact they suffer no physical

deficit in their urinary tract. What these patients need is improved access and more vigilant care. Solving their problem doesn't mean fixing their anatomy—it's a matter of logistics.

Some of the most difficult cases of uncontrolled urination also occur in nursing homes and also are not strictly incontinence. These involve patients with mental deficits, including Alzheimer's disease, who have healthy urinary tracts, but who do not exercise conscious control over their urination.

How many incontinent women go untreated?

We have just barely scratched the surface of the problem. Of the approximately 15 to 18 million women who suffer from incontinence, only 50,000 or so receive treatment.

Part of the problem is that urinary incontinence is a quality-of-life issue but not a deadly one. Harried primary care doctors have little time to ask the right questions—to investigate a bit. And patients are embarrassed to mention their difficulty; they think they just have to put up with it. I find the elderly especially hesitant—they are often afraid that revealing their problem will hasten the path to the nursing home. These women simply muddle along, hiding in their diapers.

Although diapers and pads are fine in the very short term for protection, women are getting the message that incontinence is a normal part of aging and that diapers are the only solution. Instead women should be getting themselves to a doctor: almost all urinary incontinence is treatable.

When we evaluate treatment success, we speak of keeping the patient dry, which is the ideal, and also of a subjective cure, in which the patient may not be bone-dry but is happy nonetheless. The bottom line is patient satisfaction. With treatment, more than 90 percent of incontinent women should be able to reach this level, and the rest should see dramatic improvements. Even with the most severe cases, we can usually reach the point where there is no longer breakdown of the skin or recurrent infections—these toughest cases are often found in women in nursing homes who don't receive adequate care.

Women need to be their own advocates. They need to demand treatment, and they need to seek a specialist. Often solving the problem of incontinence is beyond the scope of a primary care physician. By treating incontinence, we can dramatically improve women's quality of life—"turn their lives around," in the words of many patients.

What are some of the most useful treatments?

For both stress and urge incontinence, we have women do pelvic floor exercises, also known as Kegel exercises [*see box on this page*], which strengthen the muscles that inhibit urine flow. Sometimes we will combine this with electrical stimulation of pelvic muscles through a device placed in the vagina or rectum for short periods. Both these techniques can be done by women themselves after instruction by a physical therapist.

We often use medication to treat urge incontinence; there are a number of drugs available that can inhibit bladder hyperactivity. And in menopausal and postmenopausal women, hormone replacement therapy can often reduce incontinence. These women may gain relief from other types of treatments as well, including Kegel exercises; however, without an appropriate hormonal milieu, none of these approaches is likely to be optimally effective.

For stress incontinence that does not respond fully to the frontline treatments, surgical intervention is often necessary. There are many different options, but the basic idea behind most surgical techniques is to provide structural support to the base of the bladder, to correct prolapse and to stabilize the position of the urethral sphincter.

Another approach is to bulk up the urethra near the neck of the bladder, where exit of urine is controlled, as a way to increase the resistance against urine flow. We currently do this by injecting collagen into the tissue surrounding the urethra, under local anesthesia. These injections have proved reasonably effective in two thirds of women with stress incontinence, although about 23 percent of these women need a booster injection within two years at additional cost.

The point here is that no one treatment is for everyone: the regimen needs to be tailored to the patient. This is yet one more reason women should seek a specialist—the treatment alternatives are numerous and diverse.

Is there any way that women can prevent or minimize incontinence?

Women should be doing Kegel exercises long before they plan to have children and then stick with the routine during and after pregnancy. Intriguingly, it isn't pregnancy itself that causes most of the damage that results in stress incontinence; it is labor and delivery. Women who have cesarean sections often avoid problems with incontinence.

But anything that causes stress to the abdomen can exacerbate urinary incontinence. Therefore, I recommend that my patients watch their weight and keep their muscle tone good in general. I also encourage my patients to stop using caffeine and nicotine altogether, as both these substances cause bladder irritation and hyperactivity.

The evening is an especially tricky time to consume foods and drugs with diuretic effects, because the kidneys naturally produce more urine during the nighttime hours. A doctor may be able to reschedule a late dose of diuretic medication, and patients can avoid dietary diuretics at night.

Otherwise I don't usually make prohibitive lifestyle recommendations; for example, no changes in diet are going to make a dent in the problem like proper treatment will. And I don't want women to avoid activities they enjoy—the whole point here is to improve women's quality of life. This is not a situation women should put up with. They should seek care because they can be helped. SA

For more information, contact the National Association for Continence at http://www.nafc.org on the World Wide Web or call 800-BLADDER.

Kegel Exercises

A simple exercise can help both prevent urinary incontinence and minimize its effects. The goal is to work your pelvic muscles; you can find the correct ones by noting which muscles you use to stop a urine flow midstream. You won't see motion when you tense these muscles—they work internally. Once you know where the muscles are, you can exercise anytime: squeeze for a few seconds, relax for a few seconds, then repeat 10 times. Ideally, these exercises, called Kegels (named after gynecologist A. H. Kegel), should be done at least three times a day. —*M.S.*

PHOTOGRAPHS BY JEFFERY A. SALTER *SABA*

It's easy to focus on what goes wrong with the body as people age, but many women live healthy, vital lives into their 90s and beyond. We asked Gina Maranto to talk to women about what has gone right as they've grown older—and what the rest of us can learn from their experiences. ***—The Editors***

Having a Ball

Older women share tips on enjoying a long and healthy life

by Gina Maranto,
special correspondent

One day last year June Quinlan drove into the desert near Tucson to watch a friend whose skydiving team competes at meets around the world. Seeing the parachutists disporting themselves over the Arizona desert so piqued Quinlan's interest that she decided she would like to give it a try. A few weeks later she stepped out of a plane at 13,000 feet, making her maiden jump. Says the 82-year-old, 102-pound widow, "My friend Ginger came over and gave me a kiss while we were in free fall. I was not one bit scared."

In Scarsdale, N.Y., Ethel Danneman, 93, heads out several times a week to her seniors' group, bakes cookies, rereads Tolstoy and Jane Austen and, at regular meetings of a literary club called the Fezziwigs, ardently discusses the novels of Charles Dickens. In Teaneck, N.J., Bernice Smith, 75, regularly swims, does yoga and plays tournament bridge. According to her grandson, a personal trainer who runs his own gym, "It's hard to keep up with her." Florence Johnson, 81, of Ridgefield, Conn., walks or rides a bicycle daily and continues to play tennis, as she has since first taking up a racket at the Everglades Club in Florida at age 11. "I'd like to play more than I do," Johnson says, "but I'm a bit embarrassed that I've gotten so slow."

My own grandmother, a former schoolteacher, died in 1997 at age 92 and up until her last year was energetic and feisty. Although by the time she reached 90 her diminished reflexes kept her from driving, she still served as a tutor for the Memphis Literacy Council, sang in her church choir, planted her garden every spring, mowed her lawn, read her *U.S. News & World Report* cover to cover, cooked daily for herself and her younger sister, delighted in keeping up with three neighbor children, and religiously watched *60 Minutes* and *Wall Street Week*. By example, she taught everyone who knew her that old age did not have to be sedentary, bleak or isolating.

Evelyn Streifer, 78, plays tennis almost daily.

Is there a secret to keeping healthy as one ages? In talking with 14 women over age 70 and collecting stories about dozens more, I gleaned a great deal of pithy and trenchant advice yet found more exceptions than rules. From Trinidad to San Francisco, these women seemed to have just one thing in common besides longevity: they were difficult to reach because they were hardly ever at home.

Their personal and familial medical histories varied, as did their physical regimes, economic statuses, stress levels and diets. For example, Loretta Dranoff, 76, of Miami has never exercised regularly and says she never worried about what she ate (although she never smoked or drank). In 1985 her husband (and piano partner) of 46 years died. "I had a very hard time for a few years. Murray and I were really together 92 years," she says, "because we were together all the time."

Dranoff now works full-tilt seven days a week running an eponymous Miami-based foundation that sponsors an internationally renowned two-piano competition. She takes medication for high cholesterol but otherwise has no health problems whatsoever.

On the other end of the exercise spectrum, Evelyn Streifer, 78, also of Miami, walks with her husband every morning at 6:15, takes hatha yoga once a week and plays tennis almost daily. Her tennis coach, a former Olympian, "won't let

Claire Topper, 76, took up sculling when she retired.

me do anything negative. He makes me sprint twice around the court and times me." (Streifer's personal best: 35 seconds.) Some years ago Streifer had a bad attack of arthritis. She credits a change in diet—elimination of red meat and caffeine—with reversing the attack and staving off the debility ever since. Streifer says she exercises because she has always been active and finds that she feels better when she is. Six years ago she had lymphoma. "I felt I would conquer it," she says; she is now free of cancer.

"I have an open mind," Streifer continues, "and I think that helps. I'm always interested in people and what's happening and in new ideas." Streifer enjoins her peers from dwelling on their aches, pains and illnesses. "You can't talk about those things," she emphasizes. "It limits you."

Audrey Finkelstein, 82, who hosts a Thursday evening radio show on the National Public Radio station in Miami, agrees. As one ages, she observes, one needs to "have a different attitude about pain." Five mornings out of seven, Finkelstein walks two miles; the other two mornings, she lifts weights. But Finkelstein didn't always exercise. "My husband and I started walking about 25 years ago," she recounts. Now she doesn't want to stop: recently hobbled by tendinitis in her knee, Finkelstein got a cortisone shot and kept on walking.

"HEALTH IS A COMBINATION OF PHYSICAL WELL-BEING AND MENTAL WELL-BEING."

In general, she declares, "you have to stay occupied with something you enjoy doing." And as for physical activity: "You're never too old, and it's never too late to start."

To the strains of opera on the stereo in her Miami home, Claire Topper, 76, opines, "Health is a combination of physical well-being and mental well-being. One mixes with the other."

French by birth and an immigrant to New York City after World War II, Topper had long nursed a desire to learn how to scull. So, after retiring eight years ago, she took lessons and has been rowing ever since, most lately out of the Miami Beach Rowing Club. Widowed, she says she somewhat jealously guards her "aloneness," keeping close ties principally with family and friends in France. Topper rises every morning at five, feeds her two cats, Minette and Ebony, and by seven can often be found pushing off the dock for an hourlong solo row down Indian Creek.

Asked if she had any health tips for younger women, Topper replies, "Count your blessings. Be aware of your blessings and give thanks for them. Be very careful about what you say, think and

Audrey Finkelstein, 82, hosts her own radio show.

do. Life is a boomerang. What you do comes back to you."

Echoing Topper, Una Harris, 68, a grandmother who jogs three to four miles three days a week in her native Trinidad, also points to spiritual well-being as key—the cause, she believes, of her unfailing good health as she approaches 70. "God is my strength and ability," she says. "For me, health is love. You must give of your time to others and share." Harris, who has been singing all her life, continues to compose her own music and visit churches throughout the Caribbean.

Ethel Danneman, the 93-year-old Dickens lover, offers the most comprehensive counsel—her Ten Commandments of Health:

1. Marry only for love.
2. Walk a lot; walk every day.
3. Eat moderately.
4. Drink moderately.
5. Develop good friends.
6. Enjoy good books.
7. Enjoy good music.
8. Play mental games: recite the 50 states, the presidents—anything to keep your mind active.
9. Don't gossip.
10. Speak well of others.

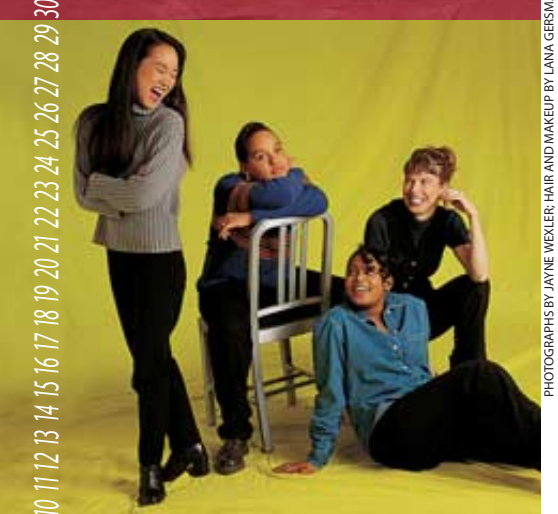
Oddly enough, several other women pointedly included admonitions against gossiping as part of their health advice. Others suggested: "Don't surround yourself with negative people." Says Charlotte Siegel, 77, who lives in North Miami, "Develop a positive attitude. Dance! Dance every day!"

Rhoda Feldman, a 76-year-old in San Francisco, tends to agree that looking on the sunny side is a good philosophy to maintain as one ages, although she finds that easy because "I'm basically a good-spirited person." But Feldman admits the evidence can be rather confounding: "I know complainers, people who are grumpy all the time, and they sometimes live longer than people who are cheerful and pleasant to be around."

Moreover, she's unwilling to generalize about other factors. She herself seems to have suffered no ill effects from having smoked for 52 years (she quit 13 years ago) or from having grown up on a rich, Russian-inspired diet (now she and her husband limit their fat intake and eat fish and emu, little red meat and lots of fruits and vegetables). To a certain extent, she speculates, longevity is just luck.

Not long ago a friend she had not seen for a few years approached her at a luncheon. "'Rhoda,' she said, 'you look so marvelous. You look so healthy. Have you had any surgery?'" Feldman says she had to think a minute before replying. "'Well, I had my appendix out when I was a child.' 'No, no,' said my friend, 'I mean have you had any plastic surgery?'" Feldman laughs. "If I don't look in the mirror, I forget how old I am."

While scientists continue to study how aging results from a combination of the assaults of the environment and the inevitability of cellular genetics, these active, vibrant women might agree on one final bit of advice: Life is too short to act your age. SA



PHOTOGRAPHS BY JAYNE WEXLER; HAIR AND MAKEUP BY LANA GERSMAN; BACKDROPS BY CHARLES BRODERSON

To Your HEALTH

From the Editors

None of the women you've seen in the photographs that open each of the four sections of this special issue is a model: they're our friends, co-workers, neighbors, relatives. When we began planning this issue, we wanted it to reflect real women and real health concerns, not just a set of dehumanized statistics. We wanted to put faces on the most up-to-date health information so that affected women—including our mothers, sisters, daughters and friends—would know they aren't alone.

Too often women take good health for granted until it's too late. They assume they won't be the ones to develop an eating disorder, have a heart attack or contract a sexually transmitted disease (STD). Many women say they're just too busy to take care of themselves: they're working late, taking the kids to the dentist or nursing elderly parents—if not all three.

But there is no excuse. Women must stop putting their own health maintenance at the bottom of the "to-do" list. Too much is at risk. As you contemplate the photographs on this page, keep in mind the following statistics:

Among women in their **teens and 20s,** two million abuse or depend on alcohol; one in four of those who are sexually active has a sexually transmitted disease; at least 25 percent smoke; and one in 12 reports that her first intercourse was nonvoluntary.

For every group of women in their **30s and 40s,** 5 percent either had no prenatal care while pregnant or received care only during the third trimester; 10 percent are battered or abused; one in nine is infertile; and fewer than one fifth exercise at least 30 minutes three times a week.

Roughly half of all women in their **50s and 60s** are overweight, have high blood pressure or have never had a mammogram.

Finally, one out of every two women **older than 70** experiences occasional urinary incontinence, has osteoporosis or suffers from arthritis.

If you recognize yourself in any of these statistics, please take a hard look at how you're treating yourself. It's time to start making time for your own well-being. SA

About the Photographer

Portrait photographer Jayne Wexler, who lives and works in New York City, says that women are among her favorite subjects. Wexler's first photo-essay book, *Daughters and Mothers*—which she wrote with Lauren Cowen—was a *New York Times* best-seller in 1997. Wexler (*first row, left, in photo at right*) was born in Brooklyn and graduated from the University of the Arts in Philadelphia, where she is now a part-time instructor. She also teaches workshops and lectures nationally.

Scientific American Presents (ISSN 1048-0943), Volume 9, Number 2, Summer 1998, published quarterly by Scientific American, Inc., 415 Madison Avenue, New York, N.Y. 10017-1111. Periodicals Publication Rate. Postage paid at New York, N.Y., and at additional mailing offices. Canadian BN No. 127387652RT; QT No. Q1015332537. Subscription rates: one year $19.80 (outside U.S. $23.80). To purchase additional quantities: 1 to 9 copies: U.S. $4.95 each plus $2.00 per copy for postage and handling (outside U.S. $5.00 P & H); 10 to 49 copies: $4.45 each, postpaid; 50 copies or more: $3.95 each, postpaid. Send payment to Scientific American, Dept. SAQ, 415 Madison Avenue, New York, N.Y. 10017-1111. Postmaster: Send address changes to Scientific American Presents, Box 5063, Harlan, IA 51593. **Subscription inquiries: U.S. and Canada (800) 333-1199; other (800) 333-1199 or (515) 247-7631.**