



# Women's *Health*

i n t h e U . S .

Research on Health Issues Affecting Women



National Institute of Allergy and Infectious Diseases

NATIONAL INSTITUTES OF HEALTH

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**NIH Publication No. 02-4697**

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## Executive Summary

A number of diseases affect women at a disproportionately high rate. Many of these are infectious, immunologic, and allergic diseases that fall under the mandate of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health. The Institute conducts research, either through its own laboratories or through funded mechanisms, on a broad spectrum of these diseases. Virtually all NIAID's clinical studies on acquired immunodeficiency syndrome (AIDS), transmission of human immunodeficiency virus (HIV), autoimmune diseases, chronic fatigue syndrome, and sexually transmitted diseases (STDs) involve women.

HIV/AIDS continues to increase among women worldwide. Among women age 25 to 44 in the United States, HIV/AIDS is now the fifth leading cause of death for all women and the third leading cause of death for African American women. Women now comprise approximately 23 percent of the total number of adults and adolescents with AIDS.<sup>1</sup>

NIAID researchers are conducting numerous studies of HIV and women, including studies to shed light on how women acquire HIV. These studies have shown that many factors—including viral load, STDs, alcohol use, crack or cocaine use, history of childhood sexual abuse, and current domestic abuse—are associated with increased risk of heterosexual transmission of HIV.

Mother-to-infant transmission of HIV—which can occur during pregnancy or childbirth or through breastfeeding—accounts for more than 90 percent of all cases of childhood HIV infection, especially in countries where effective antiretroviral therapies are not available.

According to the Centers for Medicare & Medicaid Services ([www.hcfa.gov/hiv](http://www.hcfa.gov/hiv)), of the 18 million women in the United States eligible for Medicaid, approximately 32,000 are infected with HIV; of those, about 3,000 are pregnant. Virtually all new infections in children are transmitted perinatally. Needless to say, as more women of childbearing age become infected, the number of children infected with HIV also is expected to rise.

Several NIAID-funded clinical research networks are examining various treatment regimens and prevention strategies.

NIAID has also taken the lead on tackling another vexing issue for women—autoimmune diseases, which include systemic lupus erythematosus (SLE), rheumatoid arthritis, and multiple sclerosis. Although many autoimmune diseases are rare, collectively these chronic diseases afflict 5 to 8 percent of the U.S. population and disproportionately affect women. Specifically, 90 percent of the nearly 2 million Americans diagnosed with (or suspected of having) SLE are women. SLE damages multiple tissues and organs and may affect muscles, skin, joints, and kidneys, as well as the brain and nerves.

NIAID and the National Institute for Nursing Research are cosponsoring a large-scale clinical trial of cognitive behavioral therapy and graded exercise in patients with chronic fatigue syndrome (CFS) patients, and NIAID continues to support three CFS Cooperative Research Centers.

An estimated 15 million new cases of sexually transmitted diseases occur in the United States each year. Although some STDs (e.g., syphilis) have declined to all-time lows, others (e.g., genital herpes, gonorrhea, chlamydia) continue to spread through the population, posing a significant public health problem.<sup>2</sup> Because symptoms in women are minor or nonspecific, especially in the early stages, STDs in women sometimes are not diagnosed until late in the disease. STDs that occur during pregnancy also can affect the fetus or newborn. About one-quarter to one-half of women infected with an STD during pregnancy give birth to either premature or low-birth-weight infants. In about one-third to two-thirds of these pregnancies, the infection is passed to the infant, which may cause permanent disabilities. Chlamydia, gonorrhea, and other infections of a woman's upper reproductive tract also can complicate pregnancy.

NIAID's multidisciplinary research strategy to address the complications of STDs includes basic science, vaccine development, behavioral science,

development of topical microbicides, and development of rapid and inexpensive diagnostic tests. As research increasingly connects the risk of HIV transmission to the presence of STDs, NIAID has continued research into the biological, biochemical, and behavioral basis of various STDs, as well as their manifestations and potential treatments. NIAID supports STD research through grants to individual investigators, a variety of research programs, STD Cooperative Research Centers, the Institute's STD Clinical Trials Unit, and NIAID's Topical Microbicides Program Projects.

An estimated 3 million new infections of *Chlamydia trachomatis* occur each year. Investigators at NIAID's Rocky Mountain Laboratories are studying the immune response to chlamydial infection and conducting preclinical testing of candidate vaccines. With frequent noninvasive urine-based screening, NIAID scientists have determined that 24 percent of high-risk youths are infected with chlamydia, and more than 15 percent become reinfected within a 6-month period.

About one in five adults in the United States has genital herpes, but only one-third of those people know they have the virus. Although most genital herpes cases present no symptoms, asymptomatic individuals can transmit herpes simplex virus (HSV) to others, and a pregnant woman infected with HSV can transmit the virus to her baby. Between 20 percent and 60 percent of U.S. women of childbearing age have been infected with genital herpes,<sup>3</sup> posing a significant risk of neonatal herpes. NIAID is currently investigating prevention methods, including antiviral drugs, monoclonal antibodies, and vaccines. Because about 45 to 60 million people in this country have genital herpes, these studies are important to assess the role of antiviral suppressive therapy in decreasing herpes transmission. The evaluation of monoclonal antibodies as part of a concomitant therapeutic regimen for babies with neonatal HSV infection also could help battle the persistent problem of neonatal herpes, which is still a life-threatening infection despite the availability of antiviral therapies. NIAID researchers are focusing on two major viral processes in their efforts to discover new targets for anti-HSV therapies: viral binding and entry into the host cell and viral DNA replication.

An infected pregnant woman may transmit gonorrhea to her infant during childbirth, which can result in gonococcal infection of the baby's eyes, throat, or respiratory tract. A high priority for NIAID is to develop tools to prevent gonorrhea and to gain new insights into the disease's pathogenesis, paving the way for opportunities for new diagnostic, drug, vaccine, and microbicide developments.

At any one time, an estimated 20 million people in the United States have genital human papillomavirus (HPV) infections that can be transmitted to others. Studies show high levels of HPV infection in women, with highest levels in the younger age groups.

Although sexual activity is the most common way to transmit syphilis, pregnant women with the disease can pass the bacterium to their unborn children, which may cause serious mental and physical problems. NIAID is currently supporting a clinical research protocol examining a single oral dose of therapy for early syphilis.

NIAID's research to develop topical microbicides to kill STD pathogens, including HIV, includes basic research, preclinical product development, and clinical evaluation. The Institute supports six Topical Microbicide Program Projects and recently initiated the Microbicide Preclinical Development Program. This year, NIAID also sponsored the third Topical Microbicide Preclinical Workshop to assess the state of current knowledge about preclinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV.

In all clinical research, including biomedical and behavioral studies, NIAID complies with the 1993 NIH *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. Congress mandated the establishment of these guidelines in the NIH Revitalization Act of 1993, and NIAID staff members participated in their development. The guidelines stipulate that women and members of minority groups must be included in all NIH-supported research projects involving human subjects, unless there is a compelling reason that such inclusion would be inappropriate. The guidelines also state that women of childbearing

potential should not be routinely excluded from participation in clinical research.

In addition to funding research, NIAID supports conferences, meetings, and workshops. The Institute communicates not only research results to scientists through workshops and conferences, but also medical

information to the general public and physicians through its Office of Communications and Public Liaison. Every year, approximately 12,000 people call NIAID for information and thousands more write for copies of pamphlets and other materials.

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## Acquired Immunodeficiency Syndrome

First reported in the United States in 1981, acquired immunodeficiency syndrome is caused by human immunodeficiency virus, which destroys CD4+ T lymphocytes that are critical in immune system functioning. This loss of CD4+ T cells impairs the body's ability to fight off infections and certain cancers.

HIV is spread most commonly during sexual intercourse with an infected partner. Several factors put women at risk of acquiring HIV, including substantial mucosal exposure to seminal fluids, prevalence of nonconsensual sex, sex without condom use, and unknown risk behaviors of sexual partners. HIV also can be transmitted by contact with infected blood, most often by sharing needles or syringes. In the United States, the risk of acquiring HIV from blood transfusions is now extremely small because all blood products in this country are screened routinely for evidence of HIV. In addition, the virus can be transmitted from pregnant women to their offspring during pregnancy, birth, or breastfeeding. Although the availability and use of effective antiretroviral therapies has dramatically reduced mother-to-infant transmission of HIV in the United States, this type of transmission continues to contribute to the escalating number of people suffering from AIDS on a global scale.

Worldwide, the number of women infected with HIV is increasing. As of December 2000, the World Health Organization reported that 16.4 million women (or 47 percent of all people with AIDS) were living with HIV/AIDS worldwide. In the United States, approximately 130,104 (or 17 percent) of reported AIDS cases were among women. Another 4,337 cases were reported in girls under age 13.

Women suffer from many of the same complications of AIDS that afflict men as well as gender-specific manifestations, such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, severe herpes infections, gender-specific abnormalities related to infection with human papillomavirus, and carcinomas of the vulva and vagina.

Women also exhibit different characteristics of the same complications of antiretroviral therapy experienced by men, such as lipodystrophy and fat redistribution.

The incidence of AIDS is increasing more rapidly among women than men. From 1985 to 1998, the proportion of AIDS cases in U.S. women reported each year increased from 7 percent to 23 percent. This proportion remained at 23 percent in 1999, possibly reflecting the success of antiretroviral therapies in preventing the development of AIDS; however, it was once again on the rise and reached 25 percent between 1999 and 2000.

AIDS affects minority women at a disproportionately high rate. African Americans and Hispanics constitute 77 percent of AIDS cases among women, compared to 52 percent of AIDS cases among men.

### Transmission of HIV to Women

The World Health Organization estimates that more than 80 percent of adult HIV infections worldwide are due to heterosexual transmission. This is also the main source of infection for women in the United States. In 2000, of all U.S. women infected with HIV, 38 percent became infected through heterosexual contact with HIV-infected men and 25 percent contracted HIV from using a contaminated syringe.

In the United States, studies have shown that during unprotected heterosexual intercourse with an HIV-infected partner, women have a greater risk of becoming infected than do men. In other parts of the world, however, this is not necessarily true, possibly due to a lack of circumcision in men.

A recent study conducted by the HIV Prevention Trials Network among heterosexual couples, in which one individual was HIV-positive and the other uninfected, showed that viral load is the main predictor of risk of heterosexual HIV transmission. The study found that transmission is rare among persons with viral loads below 1,500 copies of HIV-1 RNA per mL. The challenge facing researchers is to use this

information to develop prevention strategies that will slow the continued spread of HIV.

Studies in both the United States and abroad have demonstrated that STDs, particularly infections that cause ulcerations of the vagina (e.g., genital herpes, syphilis, chancroid), greatly increase a woman's risk of HIV infection. NIAID-funded cohort studies in the United States also found a number of other factors associated with increased risk of heterosexual transmission of HIV, including alcohol use, history of childhood sexual abuse, current domestic abuse, and use of crack or cocaine.

### **Natural History and Epidemiological Research**

The Women's Interagency HIV Study (WIHS), established in 1997, is a multicenter, longitudinal study designed to examine the natural history of HIV infection in U.S. women. The study is cosponsored by NIAID, the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Cancer Institute, and the National Institute of Dental and Craniofacial Research.

WIHS operates in tandem with the HIV Epidemiology Research Study, funded by the Centers for Disease Control and Prevention. The study is currently expanding to examine the natural history of HIV among women in an era of highly active antiretroviral therapy (HAART). This expansion will enable researchers to evaluate clinical outcomes in the context of HAART, such as time to AIDS, impact of other infections (e.g., hepatitis C virus), treatment and its effects in women, impact of aging on HIV, and impact of hormonal factors on HIV. WIHS also supports research on HIV pathogenesis, including HIV virology, HIV resistance to antiretroviral drugs, illicit drug use and HIV resistance to antiretroviral therapy, human papillomavirus infection, and associated cervical and anal cancers.

Recently one study in WIHS examined the HIV level in the female genital tract and its impact on transmission to sexual partners and infants. Researchers determined that women with high viral loads were more likely to have detectable levels of

HIV in their genital tract and that reductions of HIV in the genital tract could have a significant impact on HIV transmission.

In another study, WIHS researchers showed that a baseline measurement of serum albumin (the main protein in blood) was a strong predictor of 3-year survival in HIV-infected women. Women with low serum albumin levels had a higher risk of death compared to those with higher levels. This information could have important implications for women's treatment decisions. Given its availability and low cost, serum albumin measurement may have widespread applications.

Another study, conducted by WIHS and the Multicenter AIDS Cohort Study, the largest cohort of HIV-infected men in the United States, evaluated the differences in viral load and disease progression by gender, race, and history of injection drug use. The study found that HIV viral loads were 20 percent lower in women than in men although CD4+ T cell counts declined more rapidly in women than in men. Ongoing research will determine whether these disparities result in differences in clinically relevant outcomes. To date, measurements of time to AIDS and time to death have not shown differences by race or gender.

A workshop on gender and viral load—held by NIAID in conjunction with the NIH Office of AIDS Research, the National Institute of Child Health and Human Development, and Project Inform in January 2000—concluded that women tend to have lower viral loads than men in the early stages of HIV infection. The biological basis for this finding needs further elucidation. Additional information is still needed on male-female differences in the total number of lymphocytes, lymphocyte turnover or distribution, and the impact of hormonal cycles on viral and cellular dynamics.

### **Treatment Research in HIV-Infected Women**

Data from WIHS and other studies, in combination with basic research, provide the foundation for studying therapeutic interventions.

Several NIAID-funded clinical research networks—the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA)—conduct studies of various treatment regimens. In addition, NIAID intramural scientists conduct clinical studies at the NIH Clinical Center. All these clinical trial networks identify and evaluate different strategies for treating women and their infants and for preventing perinatal transmission. Each network is committed to ensuring the inclusion of HIV-infected women in clinical trials and conducting research on HIV-associated conditions that affect both pregnant and nonpregnant women. Toward that end, these programs are committed to identifying real or potential barriers to recruiting and retaining women for participation in each of these clinical trials.

During FY 2001, 953 women participated in AACTG studies, 3,229 in PACTG studies, and 800 in CPCRA studies. Respectively, women accounted for 15.4 percent, 41.6 percent, and 18.8 percent of patients in studies in each of these clinical research groups.

These clinical research networks test therapies to treat HIV infection, evaluate therapies to treat complications of opportunistic infections and other diseases that often accompany HIV infection, and conduct gender-specific studies. Because HIV suppresses the immune system, the body is hampered in its ability to resist infection. Women often develop different opportunistic infections than do men. For example, HIV-infected women frequently develop candidiasis, or yeast infections, of the mouth, vagina, and throat. These infections are persistent and difficult to treat, often increasing in severity as the immune system weakens.

Some studies currently under way are described below.

- AACTG 5029 will determine whether gender and racial differences exist in the efficacy and toxicity of medications (e.g., lipid-lowering agents, oral hypoglycemic drugs, ribavirin) commonly used to treat HIV and its complications.

- The AIDS Clinical Trials Group (ACTG) Longitudinally Linked Randomized Trials, a long-term followup study, will help determine the effect of gender and baseline viral load on disease progression and treatment efficacy, toxicity, adherence, and long-term outcome of antiretroviral therapy. This study also will determine the best initial and sequential regimens for HIV treatment and differences by gender, race/ethnicity, and age.
- AACTG 5093 will evaluate whether control of HIV replication is altered by the hormonal milieu including hormonal therapy (contraceptive or replacement) or female life cycle (adolescence, menstrual cycle variability, pregnancy, or menopause). The study will examine the effects of HIV disease progression and antiretroviral therapy on female reproductive function, hormonal status, and contraceptive efficacy.
- AACTG 5077 will identify gender differences in the rate of HIV clearance and viral decay kinetics in treatment-naïve persons and the impact on long-term treatment outcome.
- AACTG 5095 will identify gender differences in quality of life, health status, and adherence among patients enrolled in AACTG trials.

Other studies in various stages of development include a study to examine changes in HIV viral load among men and women enrolled in treatment trials; a study to examine the effects of hormone replacement therapy on HIV disease and antiretroviral treatment complications including bone density, cardiovascular disease, and neurologic function (e.g., dementia); and a study to determine the optimal long-term management of HIV in women during and following pregnancy as well as whether pregnancy alters the efficacy, toxicity, and pharmacokinetics of antiretroviral therapy.

AACTG has established four working groups with gender-specific research objectives on their scientific agendas. The Human Papillomavirus Working Group addresses issues involving HIV and human papillomavirus co-infection. The Genital Secretions Working Group studies the effect of HIV in genital fluids and the relationship to HIV transmission. The Metabolic Working Group examines the metabolic complications or effects caused by antiretroviral drugs. The Mucosal Immunity Working Group investigates

the effects of HIV infection on the immune system and mucosal tissues. This working group recently completed studies related to measuring cytokine levels in vaginal secretions; the method of measurement is now available for use in clinical studies.

In addition, the AACTG Pharmacology Committee is now developing assays to measure drug levels in genital secretions for use in studies to explore the relationships between blood and local (genital) drug concentrations, HIV transmission, and viral rebound.

### **HIV Transmission From Mother to Infant**

In the United States and other developed countries, the transmission rate of HIV from mothers to their newborn infants ranges between 15 percent and 25 percent of women who do not receive zidovudine (AZT) or a combination of antiretroviral therapies. This translates to about 1,000 to 2,000 HIV-infected infants born each year. The risk of mother-to-infant transmission is significantly higher if the mother has advanced HIV disease, large amounts of HIV in her bloodstream, or lower than normal counts of CD4+ T cells.

In 1994, NIAID supported a clinical trial, known as ACTG 076, that demonstrated that administering AZT to HIV-infected women during pregnancy and delivery and to their babies during the first weeks of life reduced the risk of maternal-to-fetal HIV transmission from 25 percent to 8 percent. This study resulted in publication of *Public Health Service Guidelines on the Use of Zidovudine (AZT) to Reduce Perinatal Transmission of HIV*.

Several NIAID-funded studies are conducted through PACTG, a large clinical trials network for HIV/AIDS research in children and adolescents, and through the Women and Infants Transmission Study (WITS), a prospective cohort study that has been following HIV-infected mothers and their children since 1988. The researchers are examining factors that contribute to perinatal transmission, evaluating disease progression and contributing factors during pregnancy and postpartum in HIV-infected women and their infants, and evaluating diagnostic tools for determining

HIV status in infants. Sponsored by NIAID, the National Institute of Child Health and Human Development, and the National Institute on Drug Abuse, WITS is examining cohorts in Chicago, Boston, New York, Houston, and San Juan.

In the past several years, PACTG and WITS have reported reassuring safety information about the use of AZT during pregnancy to prevent mother-to-infant HIV transmission. Nonetheless, concerns have been raised that antiretroviral regimens may be associated with an increased risk of premature births or severe mitochondrial dysfunction in exposed infants. To address this, a consortium of WITS investigators reviewed information on nearly 3,400 deliveries. They concluded that preterm delivery was not significantly associated with combination antiretroviral therapy with or without protease inhibitors and that deaths of children under age 5 were not attributable to illnesses that resembled mitochondrial disorders.

Although the success of ACTG 076 and other antiretroviral regimens has been documented in the United States, logistical issues and costs preclude the global use of AZT to prevent mother-to-child transmission of HIV. Unfortunately, the standard AZT regimen used to prevent perinatal HIV transmission in the United States is too expensive and impractical for widespread use in developing countries where many women may not receive prenatal care. As a result, researchers are attempting to find new interventions and simpler regimens to reduce the transmission rate around the world. Many of these studies are being conducted at domestic or international sites and are jointly sponsored by NIAID and other Federal agencies, in collaboration with other countries.

Research on perinatal transmission is particularly important in developing countries, where a large proportion of pregnant women are infected with HIV. In urban areas of Africa, for example, as many as 30 percent of pregnant women are infected with HIV; among these HIV-infected women, HIV transmission to infants is as high as 40 percent. Although more than half of mother-to-infant transmission of HIV probably occurs late in pregnancy or during labor and delivery, a substantial proportion results from

breastfeeding, the almost universal means of infant feeding in many areas of the developing world.

To overcome some of the logistical and cost obstacles with AZT disbursement in developing countries, shorter regimens of AZT were given to women a few weeks prior to and during labor, which resulted in a reduction in HIV transmission from mother to infant of 38 percent to 50 percent. In addition, researchers in the HIV Prevention Trials Network initiated a study that has identified a safe, highly effective drug regimen for preventing HIV transmission from an infected mother to her newborn that is more affordable and practical than any other examined to date. The interim results from this important study demonstrated that a single oral dose of the antiretroviral drug nevirapine given to an HIV-infected woman in labor and another to her baby within 3 days of birth reduces the transmission rate by half compared with a similar short course of AZT. Although the initial study evaluated infants at 14 weeks, a subsequent study reported that although some new HIV infections occurred in infants from breastfeeding, the overall efficacy of this intervention was maintained through the first year of life. If implemented widely in developing countries, this intervention has the potential to prevent some 300,000 to 400,000 newborns per year from beginning life infected with HIV.

Based on average U.S. wholesale costs, nevirapine is approximately 200 times less expensive than the long course of AZT used in the United States, and it is nearly 70 times less expensive than a short course of AZT given to the mother during the last month of pregnancy.

Understanding the risk of HIV transmission through breastfeeding is essential for advising HIV-infected mothers as well as for formulating public health policies. A recent NIAID-supported study discovered that although an infant's risk of becoming infected with HIV through breastfeeding is highest

during the first few months of life, the risk remains as long as the mother breastfeeds. This study was conducted among HIV-infected mothers and their babies in the African nation of Malawi. Breastfeeding is the recommended method of infant feeding in Malawi and other developing countries where alternatives to breast milk are often scarce, unsafe, or culturally unacceptable.

Early weaning has been proposed as one possible strategy to limit HIV transmission through breast milk. Although discontinuing breastfeeding after 6 months would have prevented half the HIV infections in the study, such an approach also would have increased the risk for illness and death from the respiratory and diarrheal diseases against which antibodies and other factors in breast milk help protect.

The researchers concluded that breastfeeding recommendations for HIV-infected women in developing countries must carefully balance the risk of HIV transmission with the well-known nutritional and health benefits of breastfeeding. Therefore, recommendations should be made on an individual basis because communities in developing countries include women from varied socioeconomic strata who have different access to safe milk alternatives. In the United States, where safe alternatives to breast milk are plentiful, HIV-infected women are advised against breastfeeding their infants.

Studies continue to shed light on factors that contribute to perinatal transmission, such as maternal viral load during pregnancy. An important WITS study showed that viral load predicts the risk, but not the timing, of HIV transmission from pregnant women to their infants. However, WITS researchers cautioned that women with low or undetectable viral loads should not be falsely reassured; instead they should be offered AZT therapy because of its demonstrated efficacy in reducing the risk of transmission regardless of maternal HIV levels.

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# Immunology and Immune-Related Diseases

The immune system is important at all stages of life in fighting disease-causing micro-organisms or pathogens, including viruses, bacteria, fungi, and parasites, and is able to discriminate self from nonself. A more comprehensive understanding of the immune system's role in the regulation and dysregulation of pregnancy and fertility will assist in the treatment of reproductive, gynecologic, and obstetric maladies; broaden contraception development; and advance fetal, child, and maternal health. In addition, increased understanding of the mechanisms of natural maternal-fetal tolerance may allow the development of new strategies for the induction of clinical tolerance in transplantation and autoimmune disease.

Immune-mediated diseases include a range of disorders whose basis is dysfunction of the immune system, including autoimmune diseases, asthma and allergic diseases, and primary and secondary immunodeficiency disorders. Autoimmune diseases, in which the immune system attacks the body's own tissues, affect an estimated 5 to 8 percent of the U.S. population and disproportionately affect women. These diseases can be divided into two main groups: organ-specific and non-organ-specific diseases. Organ-specific diseases are characterized by immune reactions and tissue damage localized to a single organ or tissue. Examples include type 1 diabetes and multiple sclerosis, where the primary lesions are localized in the pancreas and the central nervous system, respectively. Non-organ-specific diseases, such as systemic lupus erythematosus, are characterized by immune reactivity against antigens distributed throughout the body, resulting in widespread damage. Autoimmune diseases are believed to arise from the combined influences of environmental exposure and genetic background.

Because of their chronic nature and debilitating complications, autoimmune diseases can exact high medical and socioeconomic costs. Treatment strategies for autoimmune diseases are directed at restoring the normal immune response, preventing further tissue and organ injury, and limiting or preventing complications such as infection. NIAID supports basic, preclinical, and clinical research on immune-mediated diseases,

including studies on autoimmunity and autoimmune diseases.

## Autoimmune Diseases

Physicians and scientists have identified more than 80 distinct autoimmune diseases. The social and financial burden of these chronic, debilitating diseases can be significant and includes poor quality of life, increased health care costs, and substantial loss of productivity, particularly for women of working and childbearing age.

NIAID places a high priority on research in autoimmunity and autoimmune diseases and supports a broad portfolio of basic, preclinical, and clinical research aimed at understanding the pathogenesis of autoimmune diseases, investigating new ways to modify the immune system, and applying this knowledge to the identification and evaluation of promising approaches to treat and prevent these diseases. The past two decades of intensive and highly productive research on the immune system have resulted in a wealth of new information and extraordinary growth in conceptual understanding of the immune system. These accomplishments now provide promising opportunities for major advances in the diagnosis, treatment, and prevention of autoimmune diseases.

### *Advances in Autoimmune Disease Research*

Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms that underlie lack of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic research provides the rationale for developing clinical tests to diagnose autoimmune diseases, therapies to prevent autoimmune diseases, and novel treatments for ongoing disease. Research on any given autoimmune disease may provide information that is important for understanding other immune-mediated diseases.

Although autoimmune diseases disproportionately afflict women, systemic lupus erythematosus (SLE),

scleroderma, and multiple sclerosis (MS) have a particularly high prevalence in women. In MS, the immune system attacks proteins within myelin (the insulating sheath that surrounds the long extensions of nerve cells), destroying the myelin and greatly slowing the transmission of nerve signals, causing “short circuits” between adjoining nerve cells. These disruptions cause the symptoms of MS, such as weakness in the limbs and sensory disturbances. In SLE, the body produces antibodies that bind to various antigens throughout the body, forming complexes that provoke inflammatory responses. Deposition of these immune complexes in small blood vessels and tissues, in turn, damages the skin, joints, and internal organs, causing multiple symptoms throughout the body. Scleroderma involves the abnormal growth of connective tissue, which supports the skin and internal organs. Localized scleroderma affects the skin and musculoskeletal system; systemic sclerosis may affect blood vessels and damage the heart, lungs, and kidneys.

Exactly what triggers autoimmune responses is not known, but it may involve the display of an antigen on the surface of specialized cells, known as antigen-presenting cells (APCs), which elicits an immune response. Molecules that help display antigens on the cell surfaces of APCs are called major histocompatibility complex (MHC) molecules. MHC-antigen complexes on an APC act as a flag that attracts the attention of T cells.

A T cell receptor (TCR) is a molecule on the surface of a T cell that attaches to MHC-antigen complexes on APCs. This attachment is very specific in that a particular TCR will bind to only one type of MHC-antigen complex. When an MHC-antigen complex and a TCR bind to each other, the interaction may activate the T cell, that is, cause the T cell to orchestrate immune responses aimed at the original cells containing the antigen (e.g., in the case of MS, the myelin-coated nerve cell).

The interaction between other molecules on APCs and T cells is also important for T cell activation. These molecules are known as costimulatory molecules. When a costimulatory molecule slips into its receptor, events are triggered within the T cell that determine

whether the cell will become activated. If activated, the T cell orchestrates immune responses by attracting and activating other immune cells, in part through the interaction of cell surface molecules. In addition, the T cell may secrete chemicals known as cytokines that can attract or activate other immune cells. These activities lead to the onset of inflammatory processes that ultimately destroy the myelin in the brain and spinal cord, causing the symptoms of MS. Procedures to interrupt the molecular interactions that lead to inflammation may be useful in treating MS and other autoimmune diseases.

One treatment approach involves inhibiting the interaction between the MHC-antigen complex and the T cell.<sup>4,5</sup> Some scientists are approaching the problem from the opposite direction, creating altered cell-free versions of either the antigen or the entire MHC-antigen complex. These molecules attach to the T cell receptors on T cells—inhibiting rather than activating the cells—and may be useful in preventing the activation of T cells involved in autoimmune responses.<sup>6,9</sup>

A protein called an inducible costimulatory molecule (ICOS) was recently discovered to play a critical role in the production of most classes of antibodies. The class of antibody is determined by the type of T cell that directly activates the antibody-producing B cell, and this fate decision is mediated by ICOS. The ICOS protein is found only on activated T cells, and its binding partner, called B7RP-1, is present on B cells. An NIAID-supported investigator, among others, demonstrated the central importance of the ICOS:B7RP-1 interaction by mutating the ICOS gene to create ICOS-negative mice that have profoundly defective production of most antibody classes. Additional defects were revealed in certain cytokines, which are soluble proteins made by activated T cells that promote antibody production, but also influence inflammatory responses. Together, these results suggest that the ICOS:B7RP-1 pathway might be targeted therapeutically to enhance vaccine efficacy and to inhibit allergic or inflammatory diseases.<sup>10</sup>

Research findings suggest that low levels of estrogen may increase susceptibility to autoimmune diseases and that high levels, as seen during pregnancy,

may protect against disease, particularly in rheumatoid arthritis and MS. NIAID-supported research provided evidence that low-dose estrogen may have beneficial effects on the clinical manifestations of disease. Estrogen tablets were implanted in mice subcutaneously and mimicked high, medium, or low hormone levels. Experimental autoimmune encephalomyelitis (EAE), the mouse model of MS in humans, was induced in these animals by injection of a peptide. Compared to mice given placebo, the mice that received estrogen showed a profound reduction in the clinical symptoms of disease, characterized by reduced immune cell infiltration and myelin destruction in the spinal cords and by diminished severity of paralysis. However, estrogen was unable to ameliorate the clinical disease when administered to mice that already had developed the disease.<sup>11</sup> These studies challenge the idea that normal estrogen levels confer increased susceptibility to disease. Additional studies are needed to determine the basis of the increased incidence of autoimmune disease in women.

In autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and type 1 diabetes, chronic inflammation causes serious injury to many tissues and organs. Although many anti-inflammatory drugs are available, they generally have undesirable side effects. Previous research from many laboratories identified one of the key controllers of inflammation within cells of the immune system, a molecule known as nuclear factor kappa B (NFκB). Now, a NIAID-supported scientist, in collaboration with others, has analyzed the molecular structure of regulatory molecules that affect the activation of NFκB and designed a specific inhibitor based on this structural information. *In vivo* studies revealed that the synthetic inhibitor blocks inflammation in two mouse models of inflammatory disease. This is a critical finding for the development of new therapeutic approaches for the treatment of autoimmune diseases.<sup>12</sup>

SLE is characterized by the production of antibodies that recognize proteins from the cell nucleus. These antibodies form complexes with nuclear proteins and become trapped in the kidneys, leading to inflammatory kidney disease. An NIAID-supported investigator, in collaboration with others, showed that C-reactive protein (CRP), produced

during inflammation, promotes the clearance of nuclear proteins, directing them to the liver, where they are degraded and kept away from the kidney where they can cause disease. In SLE patients, CRP levels remain low during disease flares, suggesting that improper clearance of nuclear proteins contributes to SLE-related kidney disease. The investigator recently resolved a longstanding debate by identifying the high affinity receptors for CRP. Moreover, he found that a genetic variant of the CRP receptor, associated with susceptibility to SLE-related kidney disease, binds CRP differently than a genetic variant of the receptor that is not associated with SLE-related kidney disease. This newly described role of CRP and CRP receptors in SLE indicates a novel target for the development of new treatments.<sup>13</sup>

Systemic lupus erythematosus is an autoimmune disease characterized by high levels of antibodies directed against the body's own tissues (autoreactive antibodies). Some of these antibodies, the anti-dsDNA antibodies, deposit in the kidneys and lead to kidney failure. Women, who are disproportionately afflicted with SLE, produce higher levels of antibodies than do men. NIAID-supported research provides evidence that estrogen, the female sex hormone, may contribute to these differences. Using an animal model of SLE, autoreactive B cells, which are normally inactive, show enhanced binding capacity and produce high levels of antikidney antibodies in animals treated with estrogen. A NIAID-supported scientist demonstrated that under the influence of estrogen, the B cells express high levels of a molecule critical in B cell survival, called Bcl-2, that allows these cells to escape death and survive in the blood. This study elucidates a mechanism by which estrogen may contribute to the survival and activation of autoreactive B cells capable of producing disease-causing antibodies. Expansion of these studies to humans is needed to determine if similar mechanisms may contribute to the increased susceptibility of SLE in women.<sup>14</sup>

Novel strategies to treat or prevent the development of autoimmune disease in animal studies include vaccination to induce regulatory T cells, a component of the immune system that inactivates the disease-causing T cells. In an animal model of multiple sclerosis, NIAID-supported research previously showed

that administration of a protein, BV8S2, will induce regulatory T cells and thus prevent the development and severity of disease in male mice. However, the same treatment in female mice is only partially effective, with delayed onset but eventual development of severe disease. In recent studies, NIAID-supported scientists demonstrated that administration of the protein vaccination provides full protection in female mice in the presence of supplemental estrogen. Full protection from disease was not observed in female mice treated with either BV8S2 vaccination or estrogen alone. This study demonstrates the profound effect of estrogen on immune therapy for autoimmune disease in females and may have implications for the development of improved treatment and prevention strategies.<sup>15</sup>

#### *NIH Autoimmune Diseases Coordinating Committee*

Both House and Senate FY 1998 Appropriations Committee reports expressed congressional interest in autoimmune diseases, encouraging the establishment of an NIH Autoimmune Diseases Coordinating Committee (ADCC). This committee was established in June 1998, under the direction of NIAID. Committee members include representatives of 17 NIH Institutes, Centers, and Divisions; the Food and Drug Administration; the Department of Veterans Affairs; the Centers for Disease Control and Prevention; and private organizations that support research in this area. ADCC facilitates maximum coordination among groups working in areas of complementary and shared interests. ADCC's first report, published in December 2000, provides further details on the individual initiatives, sponsors, and current and planned research on autoimmune diseases. The report is located at [http://www.niaid.nih.gov/dait/pdf/adcc\\_rev.pdf](http://www.niaid.nih.gov/dait/pdf/adcc_rev.pdf).

As described in the Children's Health Act of 2000 (P.L. 106-310), in FY 2001, ADCC began developing a strategic plan for research on the epidemiology and burden of disease; etiology and pathogenesis; diagnosis, treatment, and prevention; and training, education, and information dissemination. It is anticipated that this research plan will be presented to Congress in spring 2002.

#### *Clinical Research Programs*

NIAID, in collaboration with other NIH Institutes, Centers, and Divisions, supports clinical research studies and clinical trials related to autoimmune diseases. The Autoimmunity Centers of Excellence (ACEs) is a cooperative research program established by NIAID to conduct pilot clinical trials of tolerogenic and immunomodulatory therapies for multiple autoimmune diseases. These Centers support a cooperative research program of integrated basic, preclinical, and clinical research, conducting single-site and multisite cooperative clinical trials for new immunomodulatory interventions and studies of mechanisms of action of tolerance induction. The clinical component will conduct pilot studies of novel immune therapies for autoimmune diseases.

NIAID established the Immune Tolerance Network (ITN), an international consortium of more than 70 basic scientists and clinical investigators, to test promising tolerogenic treatment regimens in four clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. At present, ITN is developing clinical trials involving multiple tolerance induction approaches for multiple autoimmune diseases, including multiple sclerosis and type 1 diabetes. All clinical trials will include integrated studies to identify the underlying immune mechanisms involved in disease progression and therapeutic actions of the treatment regimens. ITN is cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International. More information about ITN is available at <http://www.immunetolerance.org>.

Through the Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases, NIAID is developing clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat several severe autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and scleroderma. Studies of the underlying immune mechanisms of autoimmune diseases will be performed along with the clinical trials. More information about NIH clinical research studies is available at <http://www.clinicaltrials.gov/>.

### *Genetic Studies*

NIAID supports basic research to find the genetic causes underlying autoimmune diseases. Ultimately, this research may give physicians valuable knowledge about the basic causes of autoimmune diseases, allowing better diagnoses and treatment of patients. In FY 2000, NIAID joined several NIH Institutes and Centers and the Juvenile Diabetes Research Foundation International in supporting the International Histocompatibility Working Group (IHWG). This network comprises more than 200 laboratories in more than 70 countries that collect and share data on genes of the human leukocyte antigen (HLA) complex. IHWG is studying five diseases for which the HLA associations have been well characterized: type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthritis. In addition, NIAID supports a project within IHWG to identify single nucleotide polymorphisms in immune response genes. These variations may account for the increased susceptibility of certain individuals or groups to immune-mediated diseases.

### *Repositories and Registries*

The Multiple Autoimmune Disease Genetics Consortium is a repository of genetic and clinical data and materials from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This resource provides materials to promote research aimed at discovering the human immune response genes involved in autoimmunity. To date, 121 families have been enrolled. More information about the consortium is available at <http://www.madgc.org/>.

NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Arthritis Foundation support the North American Rheumatoid Arthritis Consortium (NARAC), a collaborative registry and repository of families with rheumatoid arthritis. The NARAC database contains 902 families, encompassing 1,522 patient visits. Data for more than half of the 902 families have been validated, including 600 affected sibling pairs. The data registry and the repository samples should facilitate the characterization of the genes' underlying susceptibility to rheumatoid

arthritis and are available to all investigators. More information about the consortium is available at <http://narak.patternrx.com>.

### *Programs and Initiatives*

To further understand the differences in the immune responses between males and females, NIAID established a new research program, Sex-Based Differences in the Immune Response, to support multidisciplinary research to identify, characterize, and define sex- and gender-based differences in immune responses. This research will include basic and clinical investigation of sex differences regulated by hormonal and nonhormonal mechanisms in response to exogenous antigens, the innate and adaptive immune response, and systemic and mucosal immunity. Awards are planned for FY 2002.

NIAID established the Cooperative Study Group for Autoimmune Disease Prevention to conduct basic research for the development of new targets and approaches to prevent autoimmune disease and to evaluate novel approaches in pilot and clinical studies. The Institute will support several investigators as part of the Gene Therapy Approaches for Diabetes and Its Complications research initiative. These investigators will conduct research on the development of novel vectors and targets in the treatment of type 1 diabetes.

In collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development, NIAID supports the Diabetes Prevention Trial—Type 1, a multisite cooperative clinical trial for the prevention of type 1 diabetes in first-degree relatives of patients with type 1 diabetes. This is the first large, nationwide trial of an immunomodulatory agent for the prevention of an autoimmune disease. The arm of this trial enrolling high-risk subjects ended early with no evidence that intervention with low-dose parenteral insulin prevented the development of disease. The intermediate-risk arm, which is testing the effectiveness of oral insulin to prevent the development of disease, is continuing to enroll participants. This trial is expected to be completed in 2004.

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## Chronic Fatigue Syndrome

People with chronic fatigue syndrome (CFS) can suffer for years from debilitating fatigue, with unrefreshing sleep, muscle and joint aches, tender lymph glands, and a host of other symptoms, including problems with mental concentration and memory. Analgesics, antidepressants, and other symptom-based therapies can provide some relief, but no known specific treatments exist for CFS. Moreover, the search for treatments is complicated by the fact that the cause of the disease is unknown. CFS is diagnosed two to four times more often in women than in men, and its onset may follow infection, stress, or trauma, which have been postulated to cause uncharacterized irregularities in the immune system, the nervous system, or the endocrine system. Early research endeavors focused on a hypothesized infectious cause. To date, no infectious or other cause has been reproducibly associated with CFS.

Prevalence and incidence rates for chronic fatigue syndrome have been difficult to obtain for several reasons, including lack of objectively verifiable diagnostic criteria, differences in case definitions used by different investigators, and potential biases related to case ascertainment. Given these factors, a large number of published studies have reported a wide range of prevalence estimates. The following data, collected by the Centers for Disease Control and Prevention from 1988 to 2001, represent surveillance-derived estimates of CFS in Wichita, Kansas. These data are available at [http://www.cdc.gov/ncidod/diseases/cfs/hot\\_topics/8.01\\_update.htm](http://www.cdc.gov/ncidod/diseases/cfs/hot_topics/8.01_update.htm).

- Weighted point prevalence at baseline was 235 per 100,000.
- Prevalence was elevated among women and highest among nonwhite women.
- CFS was rare in adolescents 12 to 17 years old.

One of the first community-based investigations designed to ascertain CFS prevalence was conducted in Seattle.<sup>16</sup> The individuals surveyed were members of a large health maintenance organization. Although older, these data are similar to CDC's more recent data mentioned above.

In 2000, NIAID and the Department of Health and Human Services CFS Coordinating Committee, respectively, held state-of-the-science workshops to evaluate the current state of CFS research and to identify promising new areas for scientific exploration. Areas addressed at these meetings included sleep disorders, neuroendocrinology, pain, cognitive disturbance, neurally mediated hypotension, immunology, and functional disability. In response to these workshops, the trans-NIH CFS Working Group, of which NIAID is a member, is developing a new Program Announcement on CFS to stimulate further research.

NIAID, along with the National Institute for Nursing Research, is cosponsoring a large-scale clinical trial of cognitive behavioral therapy and graded exercise in CFS patients. This study may provide important new information about response to treatment as well as individual host factors that may influence response in CFS.

NIAID continues to support three CFS Cooperative Research Centers, which conduct broadly focused research addressing basic science and clinical and epidemiological aspects of CFS, including its causes, characteristics, and treatment. Some highlights from these Centers are described below.

- The New Jersey CFS Cooperative Research Center is attempting to characterize heart and nervous system abnormalities in persons with CFS. In the past year, researchers have analyzed the cerebrospinal fluid of 17 patients; five had elevated protein levels. The study also is accruing data to determine whether persons with CFS have reduced cerebral blood flow.
- The University of Washington CFS Cooperative Research Center continues to examine CFS in discordant identical and nonidentical twins, obtaining other information from family members. Preliminary analyses show no differences in any of the criteria studied, with the exception of some differences in T cell activation. However, twin pairs (including healthy twins without CFS) have demonstrated remarkably disrupted sleep, poor

performance on cognition tests, and impaired exercise capacity. These findings are consistent with a neurohormonal basis for CFS. The study continues to follow the 65 patients enrolled in a the study's clinical database.

- The University of Miami CFS Cooperative Research Center focuses on cognitive-behavioral

therapy for stress management in persons with CFS. Research emphasizes the importance to patients of managing symptoms even when their causes are unknown. So far, more than 30 patients are enrolled in three cohorts, with plans to continue enrolling new cohorts every 3 months.

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## Sexually Transmitted Diseases

Sexually transmitted diseases are caused by microorganisms, or microbes, including bacteria and viruses. A crucial difference between these two types of microbes is that bacteria are one-celled organisms that can reproduce themselves, whereas viruses are extremely small organisms consisting of genetic material surrounded by a protein shell that must reproduce within host cells, using the cells' protein-producing machinery. STDs caused by bacteria include gonorrhea, syphilis, and chlamydial infection; STDs caused by viruses include AIDS, genital herpes, genital warts, and human papillomavirus (which can cause cervical cancer).

The latest estimates indicate that 15 million new STD cases occur in the United States each year, with approximately one-fourth of these new infections affecting teenagers. Although some STDs (e.g., syphilis) have declined to all-time lows, others (e.g., genital herpes, gonorrhea, chlamydia) continue to spread through the population, posing a significant public health problem.<sup>2</sup>

Most of the time, STDs cause no symptoms, particularly in women. When and if they develop, symptoms may be confused with those of other diseases not transmitted through sexual contact. Especially in the early stages of an STD, symptoms in women are minor or nonspecific. As a result, STDs in women sometimes are not diagnosed until late in the disease, with possible adverse health effects, such as poor pregnancy outcome. Other consequences include pelvic inflammatory disease (which can cause infertility) and tubal pregnancy (which occurs in the fallopian tubes).<sup>17</sup>

STDs that occur during pregnancy also can affect the fetus or newborn.<sup>18</sup> For example, death of the fetus may occur in as many as one-quarter to one-half of women infected with syphilis. About one-quarter to one-half of women infected with an STD during pregnancy give birth to either premature or low-birth-weight infants. In about one-third to two-thirds of these pregnancies, the infection is passed to the infant, which may cause permanent disabilities, such as

deafness in the case of congenital syphilis or microcephaly (abnormally small head) in the case of congenital herpes simplex virus (HSV) infection.

Among both women and men, STDs markedly increase the risk of transmitting HIV. HIV infection also may affect the natural history of STDs: diseases may progress more rapidly or be more difficult to treat. Through these interactions, STDs and AIDS amplify each other, leading to the increased prevalence of these diseases among certain populations.<sup>19</sup>

NIAID's research program on STDs has four major goals:

- To develop and license vaccines, topical microbicides, and treatments for the microbes that cause these STDs
- To understand the long-term health impact that sexually transmitted pathogens have in various populations
- To stimulate basic research on the pathogenesis, immunity, and structural biology of these pathogens
- To develop better and more rapid diagnostics.

NIAID supports STD research through research grants initiated by individual investigators and through a variety of research programs. STD Cooperative Research Centers bridge basic biomedical, clinical, behavioral, and epidemiological research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. The STD Clinical Trials Unit conducts clinical trials to test safety and efficacy of biomedical and behavioral interventions aimed at STD prevention and control. The Topical Microbicides Program Projects conduct basic research, product development, and clinical evaluation activities aimed at the development of female-controlled barrier methods to prevent STDs and HIV infection.

Knowledge of the genetic composition of STD pathogens can provide insights into the mechanisms by which they cause disease and can help identify new vaccine candidates. Therefore, NIAID supports

research to map the genes of these organisms and determine the sequence of the molecular building blocks, or nucleotides, that make up these genes. Researchers recently initiated the sequencing of the genomes of sexually transmitted pathogens including *Chlamydia trachomatis*, *Treponema pallidum*, and *Ureaplasma urealyticum*. In FY 2000, NIAID completed genomic sequences of *Neisseria gonorrhoeae* and *Haemophilis ducreyi*; the genome sequence of *Lactobacillus crispatus* (normal vaginal flora) is in progress. These genome sequences have provided new insights into the pathogenesis of these diseases, paving the way for new opportunities for diagnostic, drug, vaccine, and microbicide development.

## Chlamydial Infection

*Chlamydia trachomatis*, a bacterial pathogen, is a major cause of preventable blindness and STDs in the developing world. An estimated 3 million new infections occur each year. Moreover, cross-sectional studies and data collected from adolescent and family planning clinics have documented that adolescents age 15 to 19 have the highest rates of chlamydial infections, irrespective of socioeconomic status.<sup>2</sup>

Chlamydial infection causes most of the same syndromes and symptoms as gonorrhea (e.g., painful urination, increased vaginal discharge, abdominal pain, abnormal menstrual bleeding), although the proportion of cases with no overt symptoms is higher for chlamydial infection. Furthermore, when symptoms of chlamydia do occur, they tend to be less severe.<sup>20</sup> Both chlamydia and gonorrhea can cause urethritis (inflammation of the urethra), which can result in frequent and painful urination and the presence of white blood cells in the urine. Both diseases also can produce inflammation of different parts of the female reproductive system—including the cervix, endometrium (inner membrane) of the uterus, and fallopian tubes—leading to pelvic inflammatory disease (PID). PID symptoms include vaginal discharge, pain in the lower abdomen, pain with sexual intercourse, and abnormal uterine bleeding. Recurrent or severe PID often results in infertility or tubal pregnancy. In some cases, fallopian tube inflammation

can be “silent” or undetected, although it can still cause infertility and tubal pregnancy.

The mouse model of *C. trachomatis* infection mimics human infection and is therefore useful for studying the immune response to chlamydial infection and for preclinical testing of candidate vaccines. Investigators at NIAID’s Rocky Mountain Laboratories are using this model to learn what constitutes a protective immune response in the genital mucosal and to determine what chlamydial component is necessary to elicit this response. These studies will be useful in formulating vaccines for the prevention of chlamydial STD in humans.<sup>21,22</sup>

A major problem with controlling chlamydia is that more than 80 percent of infections are asymptomatic and frequently go undetected. The new and highly sensitive molecular diagnostic assays are more reliable than other available tests for detecting chlamydia and can utilize noninvasive specimens such as urine and self-administered vaginal swabs. NIAID-funded researchers have applied these new technologies to screening large populations in Baltimore, in the U.S. military, and in Uganda; they have documented extremely high rates of infection ranging from 5 percent to more than 25 percent. With frequent noninvasive urine-based screening, NIAID-supported scientists have determined a prevalence of 24 percent in high-risk youths and a reinfection rate of more than 15 percent within a 6-month period.

Researchers funded by NIAID plan to continue using population-based studies that incorporate newly developed molecular amplification assays to screen individuals for *C. trachomatis*, *N. gonorrhoeae*, and other STDs noninvasively. The goal is to better define the epidemiology, prevalence, and incidence of, as well as risk factors for, infection. Cost-effective models will be applied to these data, and NIAID-supported researchers will monitor the effect on the prevention of the sequelae such as pelvic inflammatory disease, ectopic pregnancies, infertility, and trachoma. Additional studies are planned to further examine the immunopathogenesis of chlamydial cervical infections in women with PID and tubal factor infertility using molecular amplification techniques.

## Genital Herpes

Herpes simplex virus type 1 (HSV-1) causes the majority of oral herpes cases, and herpes simplex virus type 2 (HSV-2) causes the majority of genital herpes cases. However, both type 1 and type 2 HSV can occur in the genitals, oral area, or both. About one in five adults in the United States have genital herpes, but only one-third of those people are aware that they have the virus. The number of Americans with genital herpes infection has increased 30 percent since the 1970s. Moreover, HSV-2 prevalence among 12- to 19-year-old whites is now five times higher than it was 20 years ago. In addition, young adults age 20 to 29 are now twice as likely to have HSV-2.<sup>2</sup>

Most genital herpes cases are asymptomatic, but infection still poses risks. Asymptomatic individuals can transmit HSV to others, although transmission may not be as efficient as when skin sores are visible. It is believed that a pregnant woman infected with HSV can transmit the virus to her baby. Usually, neonatal herpes occurs during vaginal delivery, particularly if the woman has become infected with HSV for the first time during the last trimester of pregnancy. Considering that between 20 percent and 60 percent of U.S. women of childbearing age have been infected with HSV-2,<sup>3</sup> the risk of neonatal herpes is significant.

To prevent herpes infection of the infant during delivery, a cesarian section can be performed if visible sores are detected around the mother's cervix before the placental membranes break. Other methods of prevention are currently being investigated, including antiviral drugs, monoclonal antibodies, and vaccines.<sup>3</sup>

Vaccines for genital herpes are undergoing testing. One such vaccine is an attenuated virus, meaning that the virus has been weakened through mutations so that it is able to provoke an immune response by the body but cannot cause disease. Studies have shown that the vaccine is effective in animal models and safe for humans. The second vaccine consists of an HSV surface protein plus a booster molecule called an adjuvant. Further studies are being planned to consider the efficacy of these vaccine candidates.

NIAID-funded researchers also are exploring animal model systems and technologies that test novel

DNA-based vaccines for genital herpes. Initial studies in mice have verified that DNA-based vaccines are highly protective against HSV-2 infection.

With sponsorship by private industry, NIAID researchers are conducting a randomized, multicenter, double-blind, placebo-controlled phase III study to evaluate the effect of valaciclovir in preventing herpes transmission in heterosexual couples discordant for the presence of HSV-2 antibody. A total of 1,500 couples have been randomized into the study at approximately 100 outpatient centers in the United States, Canada, and Europe. This clinical study is now closed to accrual, and patients are undergoing followup. Investigators will analyze the results over the next year.

Scientists are also studying HSV 863, a human monoclonal antibody, against herpes simplex virus. *In vitro* and *in vivo* studies showed that HSV 863 is effective both prophylactically and therapeutically against HSV. Subsequent studies are assessing the safety, potency, and pharmacokinetics of HSV 863 in an adult population before the antibody is tested as adjunct therapy for neonatal herpes. This study will be followed by a phase I/II study of HSV 863 in babies with encephalitis and disseminated neonatal HSV infection to further determine the dose to be used in a phase III controlled trial for babies with neonatal HSV infection.

Because about 45 to 60 million people in this country have genital herpes, this study is important to assess the role of antiviral suppressive therapy in decreasing herpes transmission. The evaluation of monoclonal antibodies as part of a concomitant therapeutic regimen for babies with neonatal HSV infection also could help battle the persistent problem of neonatal herpes, which is still a life-threatening infection despite the availability of antiviral therapies.

NIAID researchers are focusing on two major viral processes in their efforts to discover new targets for anti-HSV therapies: viral binding and entry into the host cell and viral DNA replication. The drugs that are currently used to treat HSV infections act by selectively inhibiting the process of viral DNA replication. NIAID scientists are studying several proteins that are involved in viral DNA replication to determine if they may be appropriate targets for more effective inhibitory

drugs. In addition, the control of HSV DNA replication in certain cell types, such as neuronal cells, is critical in the process by which HSV becomes latent in these cells. Understanding the mechanisms of latency is key to understanding how to prevent reactivation of the latent virus.

HSV attaches to and enters the host cell via a multistep process involving more than 10 viral glycoproteins and several cellular factors. Although many of these have been identified, the step-by-step process underlying viral binding and entry into susceptible cells remains unclear. Investigators are working to identify cell molecules that help in binding the virus to cells and to determine how the stable binding triggers subsequent fusion and entry into the cell. These studies are providing important insights into the biology of the virus and helping to identify new targets for therapeutic interventions.

In addition, research is progressing on the development of natural and synthetic porphyrins and metalloporphyrins (MPs). These compounds possess potent and broad-spectrum antibacterial activity. A number of porphyrin compounds have been found to have potent virucidal activity against either HSV-2 alone or both HSV-1 and HSV-2. Moreover, sodium dodecyl sulfate, a detergent found in personal hygiene products used on the skin and oral mucosa, has been found to protect mice from the morbidity and mortality associated with HSV-2 infection.

With regard to neonatal infections, investigators with NIAID's Collaborative Antiviral Study Group significantly advanced the treatment of neonatal herpes virus infections by establishing the safety and effectiveness of a new dose of the standard antiviral drug acyclovir. Despite treatment, children infected with herpes neonatally continue to die and suffer from blindness and other morbidity. To address this, researchers conducted a study to determine whether a higher dose of acyclovir could lead to improvement. This study demonstrated that administration of 60 mg/kg/day of acyclovir (double the dose currently approved by the Food and Drug Administration) significantly reduced mortality (from 61 percent to 31 percent) in newborns with disseminated HSV, the most severe form of HSV.

## Gonorrhea

Gonorrhea is caused by the bacterium *Neisseria gonorrhoeae*, also known as gonococcus. Gonococci infect the same body sites as chlamydia but may be more likely to produce symptoms. Furthermore, when they occur, symptoms tend to be more severe. Among women, the bacteria first infect the cervix; however, as with chlamydia, the bacteria can spread to the uterus and fallopian tubes, causing pelvic inflammatory disease. Symptoms associated with gonorrhea in females include painful urination, increased vaginal discharge, abdominal pain, and abnormal menstrual bleeding. In 2000, the Centers for Disease Control and Prevention estimated that more than 650,000 individuals were newly infected with gonorrhea.<sup>2</sup>

An infected pregnant woman may transmit gonorrhea to her infant as the baby passes through the birth canal during delivery. This can result in gonococcal infection of the baby's eyes, throat, or respiratory tract. Evidence suggests that gonococcal infection during pregnancy also is associated with premature rupture of the placenta and preterm delivery.

A high priority for NIAID is to develop tools to prevent gonorrhea, such as vaccines or topical microbicides (substances that could be used to coat the inside of the vagina where they would kill gonococci and other STD pathogens). The recent completion of the genomic sequence of *N. gonorrhoeae* will help provide new insights into the pathogenesis of gonorrhea, paving the way for opportunities for new diagnostic, drug, vaccine, and microbicide developments.

## Human Papillomavirus

Human papillomavirus (HPV) is likely the most common sexually transmitted disease among young, sexually active people. At any one time, an estimated 20 million people in the United States have genital HPV infections that can be transmitted to others. Each year, about 5.5 million people acquire a genital HPV infection. Studies show high levels of HPV infection in women, with highest levels in the younger age groups. Thirty distinct types of HPV can infect the

genital area. Infection with certain types of HPV has been shown to be the single most important risk factor for cervical cancer.<sup>2</sup>

In collaboration with the Los Alamos National Laboratory, NIAID has established a database of information on the genetic sequences of HPV and related papillomaviruses. In 1998, this effort was expanded and a relational database (STDGEN) was established. This includes HPV sequences as well as those genomes of other STD pathogens. The database analyzes structure and function relationships within and between pathogens. Acquisition of this genomic information will help pave the way for the development of new diagnostics, therapeutics, and vaccines.

Using the various animal models, NIAID-supported scientists have been testing a new class of antiviral drugs for their effectiveness in treating warts. The most promising candidate so far is cidofovir. On the basis of promising results in animal models, Belgian researchers treated patients with severe recurrent laryngeal papillomatosis.<sup>23</sup> These people had been infected with HPV at birth, and warts continued to grow on their larynx (voice box) into adulthood.

Because of positive results obtained in the Belgian study, NIAID's Collaborative Antiviral Study Group, a network of about 100 clinical sites throughout North America, will begin a clinical trial of cidofovir for treating recurrent laryngeal papillomatosis among children. In addition, two other NIAID-supported groups are conducting studies of cidofovir as a therapy for genital papillomavirus infection, and another NIAID-funded group is conducting a trial of the antiviral drug ribavirin as a supplement to laser surgery for treating laryngeal papillomatosis.

In a particularly significant development, NIAID-supported scientists have developed a vaccine that not only protects mice against the development of tumors similar to those that occur with cervical cancer but also cures mice with established tumors. The vaccine causes the immune system to attack an HPV protein that helps transform normal cells into cancer cells. In studies with mice, vaccination protected 80 percent of the mice from the development of tumors and cured those with small, established tumors.<sup>24</sup>

To develop better therapies for HPV infection, NIAID researchers are investigating the functions of important HPV proteins that control the replication of viral genes and the production of viral proteins and that possibly play a role in the progression of HPV-related tumors.<sup>25</sup> Understanding the role of these proteins in the viral life cycle and in cancer might lead to the design of specific antiviral therapies.

## Syphilis

Syphilis is a sexually transmitted disease caused by a bacterium called *Treponema pallidum*. The initial infection causes an ulcer at the site of infection, and the bacteria move throughout the body, damaging many organs over time. Medical experts describe the course of the disease by dividing it into four stages—primary, secondary, latent, and tertiary (late). An infected person who has not been treated may infect others during the first two stages, which usually last 1 to 2 years. In its late stages, untreated syphilis, although not contagious, can cause serious heart abnormalities, mental disorders, blindness, other neurologic problems, and death.<sup>26</sup>

The bacterium spreads from the initial ulcer of an infected person to the skin or mucous membranes of the genital area, the mouth, or the anus of a sexual partner. It also can pass through broken skin on other parts of the body. The syphilis bacterium is very fragile, and the infection is almost always spread by sexual contact. In addition, a pregnant woman with syphilis can pass the bacterium to her unborn child, who may be born with serious mental and physical problems as a result of this infection. However, the most common way to get syphilis is to have sex with someone who has an active infection.

In 1999, 6,657 cases of primary and secondary syphilis in the United States were reported to the Centers for Disease Control and Prevention. However, syphilis continues to disproportionately affect African Americans, with reported rates of primary and secondary syphilis 30 times higher for African Americans than for white Americans.<sup>2</sup>

As part of the Public Health Service's effort to eliminate syphilis in the United States by 2005,

NIAID's efforts focus on providing better biomedical tools to prevent and control this disease. These efforts include (1) diagnostic test development, which is intended to create a rapid, inexpensive, easy-to-use test that would not require a blood sample; (2) a clinical research study of oral therapy to treat early-stage syphilis; and (3) development of a syphilis vaccine that would target and prevent systemic infection (including congenital syphilis) and could potentially ameliorate disease progression.

NIAID is currently supporting a clinical research protocol examining a single oral dose of therapy for early syphilis. The goal of the study is to determine if treating syphilis with azithromycin is as effective as the current recommended treatment, benzathine penicillin G. Azithromycin offers many advantages over benzathine penicillin. Azithromycin is taken orally; benzathine penicillin is administered by injections that are often very painful and discourage patients from seeking treatment. In addition, the penicillin injections require refrigeration and needles, which can hamper administration in "field" settings. The azithromycin regimen proposed in this study could be administered as direct observed therapy in the field, using strategies modeled after those used to treat tuberculosis.

The long-term goals of all NIAID's syphilis activities are to (1) complement CDC's syphilis elimination program; (2) provide improved biomedical and behavioral tools to achieve and sustain syphilis elimination in the United States; and (3) provide improved tools for prevention and control of syphilis in developing countries. NIAID's research takes into account the limited resources of areas where syphilis is endemic, the social and cultural barriers to accessing effective health care in some of those areas, and the need for sustainable interventions.

### **Topical Microbicides**

A topical microbicide is a preparation (e.g., gel, cream, foam) that is applied to the vagina or rectum to kill STD pathogens, including HIV, being transmitted by either sexual partner. Topical microbicides might be more effective than condoms because they would be easier to use and women would not have to negotiate

their use, as they often must do with condoms. The ideal microbicide would be safe and nonirritating to the mucosal tissues, even if used on multiple occasions in a short period of time. In addition, the microbicide should be inexpensive, unobtrusive, both fast- and long-acting, easy to store, and appealing to potential users. Topical microbicides should be available in both spermicidal and nonspermicidal formulations so that women would not have to put themselves at risk for acquiring HIV and other STDs to conceive a child.

NIAID's research effort for developing topical microbicides includes basic research, preclinical product development, and clinical evaluation. The goal of this comprehensive research effort is to support research and development that leads to the identification of safe and effective topical microbicides. Toward this end, the Institute supports six Topical Microbicide Program Projects that focus on the development of these compounds and recently initiated the Microbicide Preclinical Development Program. This new program, cosponsored by the National Institute of Child Health and Human Development (NICHD), supports the discovery and preclinical development of novel or underexplored microbicides. To date, NIAID and NICHD each have made three awards. In addition, both Institutes jointly established the Integrated Preclinical/Clinical HIV Topical Microbicide Program to conduct translational research, taking promising concepts into early pilot clinical trials. It is anticipated that awards will be made in 2002.

This year, NIAID also sponsored the third Topical Microbicide Preclinical Workshop to assess the state of current knowledge about preclinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV. The workshop reviewed the progress of the Topical Microbicide Program Projects, facilitated collaborations among scientists from different disciplines and among academic and private-sector participants, and encouraged interactions between Food and Drug Administration regulatory staff and commercial sponsors. The workshop included representatives from the public and private sectors, industry, Government, foundations, and community advocacy groups.

NIAID supports large-scale *in vitro* screening of potential HIV transmission-blocking agents through a contract to the Southern Research Institute facility in Frederick, Maryland. Potential microbicides are obtained from the private sector, academic, and governmental sources, and they are tested in several different assays to determine their ability to block HIV transmission from infected T cells to cultures of cells derived from the lining of the human cervix. In the past year, a new assay was developed to monitor the activity of potential microbicides under the conditions that mimic the vaginal environment. To date, more than 1,825 unique compounds have been examined in nearly 4,200 primary and secondary assays. The colorless or lightly colored compounds with a high therapeutic index are undergoing additional evaluation to assess their potential for development as topical microbicides, to determine whether they cause intravaginal irritation or other adverse effects in experimental animals, and to ascertain whether they remain stable in the vagina after delivery.

NIAID has a contract with the University of Washington for microbicide research in nonhuman primates, which during the past year evaluated 11 candidate microbicides for safety (effects on surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques. Three of these candidates also have been tested for efficacy against chlamydial challenge in the same pig-tailed macaque model, and several are entering clinical trials in the HIV Prevention Trials Network. This large clinical trials network, with both domestic and international sites, was established to develop and evaluate nonvaccine HIV prevention strategies, including topical microbicides.

A number of promising topical microbicide candidates are in various stages of testing. BufferGel™, an acid-buffering gel, helps maintain the normal acidic environment of the vagina during coitus to disrupt the transmission of acid-sensitive STD pathogens, such as HIV. BufferGel has been tested in clinical trials through NIAID's HIV Prevention Trials Network (HIVNET) to evaluate its safety and tolerability. The first trial was conducted in the United States, followed by studies in India, Thailand, Zimbabwe, and Malawi. The results of these trials indicate that BufferGel was nontoxic and well tolerated. In a phase III trial in

Cameroon that enrolled 1,200 persons, a nonoxynol-9 film was found to have no effect on transmission of HIV, gonorrhea, or chlamydia when provided as part of an overall HIV/STD prevention program. No additional studies of nonoxynol-9 are being conducted due to safety concerns and the potential for increased risk of HIV infection reported in preliminary findings from a phase II Nagel trial during the 13th International Conference on AIDS in Durban, South Africa, in July 2000.

NIAID-supported researchers recently completed a phase I study (HIVNET 020) of PRO 2000, a synthetic compound that works by inhibiting HIV attachment and fusion. Initiated in 1999 in Rhode Island and Pennsylvania and in Durban and Johannesburg, South Africa, the study examined sexually active women at low risk of HIV infection as well as asymptomatic HIV-infected women who were sexually abstinent. The study assessed different strengths of PRO 2000 Gel administered intravaginally once or twice a day for 14 consecutive days and found that the product was well tolerated in both groups of women with no serious side effects. All the women indicated their willingness to use the product again if it were shown to protect against HIV infection. Differences in PRO 2000 concentration, frequency of use, and HIV status did not appear to be associated with differences in the prevalence of adverse events. Because PRO 2000 was safe and well tolerated (under the specific conditions of this study), NIAID will continue to evaluate it for widespread effectiveness and potential use.

NIAID is also initiating a phase I study of 9-(2-phosphonylmethoxypropyl)-adenine (PMPA), which inhibits HIV replication. PMPA gel has prevented the infection of female monkeys with simian immunodeficiency virus, a relative of HIV, when their vaginas were exposed to the virus.

A particularly novel approach to developing new microbicides involves the use of a bacterial strain called *Lactobacillus crispatus*, which naturally colonizes the vaginas of many women. These bacteria produce chemicals that kill harmful microbes, including those that cause STDs and have been shown to be associated with reducing women's risk of getting gonorrhea, HIV

infection, and bacterial vaginosis, a type of vaginal inflammation. This past year, NIAID-funded researchers initiated a study of oral metronidazole with *L. crispatus* or placebo to determine its safety and effectiveness in treating bacterial vaginosis. Other potential compounds that will continue to be examined include chemicals produced by animal cells for defense against microbes, such as the protegrins, a family of small proteins produced by the white blood cells of animals. Researchers supported by NIAID have produced several variants of one protegrin that are able to inactivate gonococci, chlamydia, and HIV without adverse effects on human cells.

To further advance topical microbicide research, NIAID will hold a workshop to address the unique aspects and complexities of conducting clinical trials to ascertain the safety and effectiveness of microbicides in international settings. In addition, a strategic plan is being developed detailing long-range plans for the whole spectrum of microbicide research, from laboratory to clinical trials. A panel of experts will review the plan within the year.

### **The Role of Sexually Transmitted Diseases in Spreading AIDS**

Compared with other viruses that cause STDs, such as herpes simplex viruses, human papillomaviruses, and hepatitis B virus, HIV is not easily transmitted. Transmission occurs in only 1 of 500 cases of vaginal intercourse in which one partner is infected. However, if either partner has another STD, this substantially increases the risk of HIV transmission. STDs that cause discharge of pus and mucus (e.g., gonorrhea,

chlamydial infection) increase the risk from threefold to fivefold, and STDs that cause ulcers (e.g., syphilis, genital herpes) increase the risk up to ninefold.<sup>27</sup>

A number of possible mechanisms may be responsible for these increases. Certainly, the ulcerative STDs disrupt the protective layers of skin and mucosa, which may allow HIV easier access to blood vessels. STDs also increase the number of inflammatory cells in the reproductive system, some of which are targets of HIV.<sup>27</sup>

Whatever the mechanisms, identifying and treating existing STDs is clearly one important strategy for reducing HIV transmission. NIAID-supported researchers have demonstrated the effectiveness of this strategy with men infected with both HIV and gonorrhea. As a result of the gonorrhea, these men had urethritis (inflammation of the urethra, the canal that carries both semen and urine). The scientists noticed that urethritis greatly increased the HIV load in the semen of these men and that treating the gonorrhea and the inflamed urethra reduced the seminal HIV load, even if the patients were not taking drugs for the HIV infection.<sup>28</sup>

Herpes simplex virus type 2 is a common viral coinfection in persons with HIV. NIAID-funded studies have suggested that the rate of HIV progression may be affected by HSV reactivation. Thus, daily suppression of HSV may be important for the management of persons with both HSV and HIV. Additional studies are required to determine the effect of HSV suppression on both the rate of HIV transmission and the natural history of HIV.

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## Glossary

**adjuvant**—A substance added to an antigen in a vaccine to enhance or modify the immune response to the antigen.

**ameliorate**—To make better or improve.

**antibody**—A protein molecule produced and secreted by immune cells in response to an antigen. The antibody binds to the antigen, triggering reactions of the immune system that are designed to eliminate the antigen.

**antigen**—Any substance that, when introduced into the body, stimulates an immune response.

**autoimmune disease**—A disease that results when the immune system mistakenly attacks the body's own tissues.

**bacterium**—A microscopic organism composed of a single cell. Many but not all bacteria cause disease.

**concomitant**—Occurring or existing concurrently; accompanying.

**culture**—The propagation of micro-organisms or of living tissue cells in media designed to support their growth.

**disseminated HSV**—Herpes simplex virus spread over a considerable area; the most severe form of HSV.

**ectopic pregnancy**—Development of an embryo in a pregnancy location other than the uterus—for example, in a fallopian tube or in the abdominal cavity.

**endocrine system**—The system of glands and other system structures that controls hormone release.

**endometrium**—The inner membrane of the uterus.

**epidemiology**—The science concerned with the factors affecting the frequency and distribution of disease for the purpose of establishing programs to prevent and control their development and spread.

**fallopian tubes**—A pair of long slender tubes that carry eggs from the ovaries to the uterus.

**gene**—The functional unit of heredity that occupies a specific place on a chromosome, is capable of reproducing itself exactly at each cell division, and directs the formation of an enzyme or other protein.

**hematopoietic**—Forming blood or blood cells in the body.

**histocompatibility**—A state or condition in which the absence of immunological interference permits the grafting of tissue or the transfusion of blood without rejection.

**hormone**—A chemical formed in one organ or part of the body and carried in the blood to another organ or part. Hormones can alter the functional activity and sometimes the structure of one or several organs.

**immune response**—The reactions of the immune system to foreign substances.

**immune system**—A complex system of cells and molecules having the primary function of protecting the body from foreign organisms and substances.

**incidence**—The rate of occurrence of a disease—for example, the percentage of people who contract a particular disease within a year.

**inflammation**—Redness, warmth, swelling, pain, and loss of function produced in response to injured tissue. Inflammation results from increased blood flow and an influx of immune cells into the injured area. It initiates the elimination of the injurious agent and the injured tissue.

**major histocompatibility complex molecules**—Cell surface molecules that help control the immune response against microbes or tumors. These molecules present antigens to nearby T cells as a flag indicating that a cell is infected or diseased.

**micro-organisms (microbes)**—Minute living organisms, including bacteria, viruses, fungi, and protozoa.

**molecule**—The smallest amount of a specific chemical substance that can exist alone. A molecule consists of one or more atoms—for example, a molecule of water consists of two hydrogen atoms and one oxygen atom.

**mucous membrane (mucosa)**—A membrane rich in mucous glands. Mucous membranes line body passages and cavities that communicate directly or indirectly with the exterior.

**mucus**—A slippery secretion produced by mucous membranes that moistens and protects the membranes.

**mutation**—An alteration of a gene or chromosome that can be inherited.

**organism**—An individual living being.

**pathogen**—A micro-organism, such as a bacterium, that lives on an animal (or plant) or human as a parasite and produces a disease.

**pelvic inflammatory disease**—An ascending pelvic infection causing inflammation of female reproductive organs, such as the uterus, fallopian tubes, and ovaries.

**perinatal**—The time shortly before and after birth.

**placebo**—An inactive substance that is given to the control group of patients in a clinical trial. The purpose is to compare the effects of medication with that of no medication.

**polymorphism**—The occurrence of different forms, stages, or types in individual organisms or in organisms of the same species, independent of sexual variations.

**prevalence**—The percentage of a population that is affected with a particular disease at any given time.

**prophylactically**—Acting to defend against or prevent something, especially disease; protective.

**proteins**—Large organic compounds composed of smaller molecules called amino acids.

**receptors, cellular**—A protein molecule, usually on the cell surface, that binds to a specific factor, such as an antigen.

**syndrome**—A group of signs and symptoms that occur together and characterize a particular abnormality.

**systemic lupus erythematosus**—An inflammatory disorder characterized by bleeding in the skin and mucous membranes, inflammation of the membrane enclosing the heart, and possibly involvement of the kidneys and central nervous system. Of unknown cause, but probably an autoimmune disease.

**T cells**—Small white blood cells that orchestrate or directly participate in immune defenses.

**tolerance**—A state in which the immune system does not respond to a particular antigen or group of antigens.

**tolerogenic**—Capable of inducing immunologic tolerance.

**topical microbicide**—A chemical that can be applied to the surface of the body to kill micro-organisms. In connection with sexually transmitted diseases, a topical microbicide would be applied in the vagina or rectum to kill the microbes that cause these diseases.

**urethra**—The canal that carries urine from the bladder to the outside. In men, the urethra also carries semen.

**vaccine**—A substance that contains antigenic components from an infectious organism. By stimulating an immune response (but not disease), a vaccine protects against subsequent infection by that organism.

**virus**—A submicroscopic microbe that causes infectious disease. Viruses can reproduce only in living cells.

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National Institute of Allergy and Infectious Diseases  
NIH Publication No. 02-4697  
March 2002  
[www.niaid.nih.gov](http://www.niaid.nih.gov)