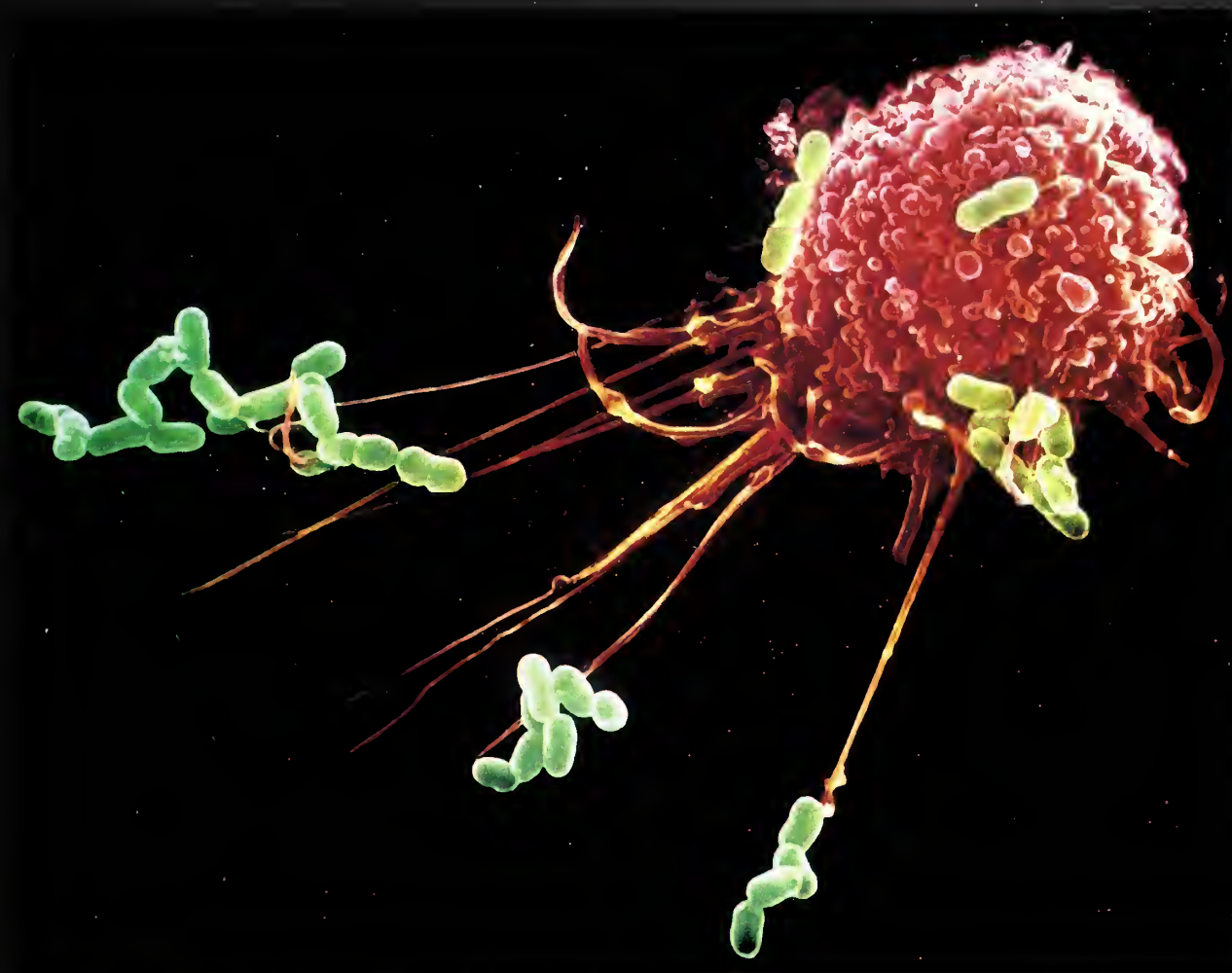


THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

THE EDGE OF DISCOVERY

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Director's Statement

The National Institute of Allergy and Infectious Diseases stands at the forefront of scientific research on countless diseases that affect not only the quality of life but threaten the very existence of millions of people.

Basic and clinical research is conducted and supported by NIAID in microbiology, infectious diseases, immunology, and disorders of the immune system, including asthma and allergies. These efforts have dramatically benefitted the health of Americans, in particular, and hold great potential for the developing world.

Challenges abound, however, as we encounter such new problems as drug resistance in malaria, the epidemic of sexually transmitted diseases, and the emergence of a deadly new disease—AIDS. Medical scientists have a keen awareness of the magnitude of human suffering caused by infectious and immunologic diseases and the great need for better ways to diagnose, treat, and prevent these illnesses.

We also have great confidence that the rapidly burgeoning fields of immunology, cell biology, and molecular genetics and the concurrent revolution in biotechnology have brought us to the edge of discovery of new answers to many medical problems.

In our search for research results that have immediate clinical application, however, we cannot overstate the intrinsic value of basic research. The history of science continually proves the far-reaching influence of researchers who are free to exercise their intellect, curiosity, and imagination in the pursuit of new scientific truths. NIAID places great emphasis on fundamental studies in our own laboratories and at the many universities and research centers that receive our support both in this country and abroad.

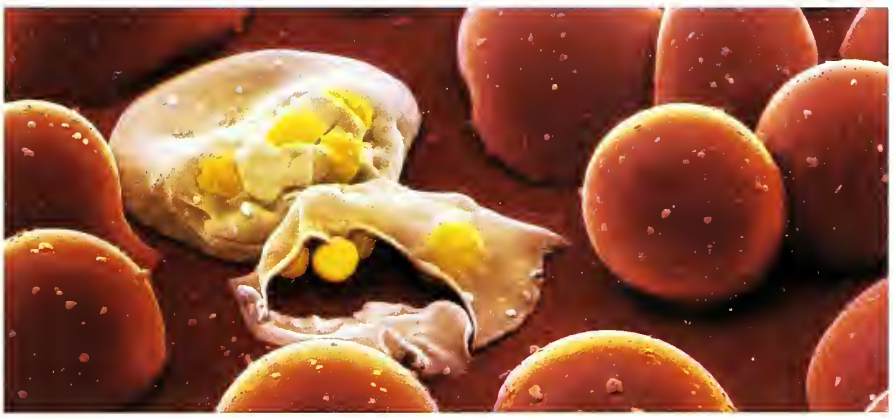
A hallmark of contemporary science is the overlapping of boundaries between disciplines and the consequent collaboration among laboratory and clinical investigators. Both in providing support for basic research and in responding to critical public health needs, NIAID initiates and supports innovative, multidisciplinary approaches.

This brochure presents some of the highlights of our programs and the areas of most avid scientific interest. As Director of NIAID, I welcome inquiries from all scientists who are interested in our programs, and who may wish to join our efforts either within the Institute or through grant or contract support. We especially encourage applications from young people, women, minorities, and the handicapped.

Anthony S. Fauci, M.D.
Director

THE EDGE OF DISCOVERY

**National Institute
of Allergy and
Infectious Diseases**



Contents

Cover: a macrophage extends pseudopods to embrace *Escherichia coli* bacteria.

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

NIH Publication No. 88-2773
June 1988

Central to the mission of the National Institute of Allergy and Infectious Diseases is the study of the immune system as it functions in health and disease. Immunology is the bedrock for the development of agents and procedures that can protect the immune system, restore damaged immune function, and suppress the immune system when it goes awry.

Numerous, interlocking steps are involved in the development and maintenance of immune responses. Aberrations in this process can result in inherited and acquired immunodeficiencies, allergies, autoimmune conditions, and other diseases. Many of these illnesses are painful and life-threatening, and exact a heavy toll in the lives of patients and their families and friends.

IMMUNOLOGY

New Knowledge Widens Research Opportunities

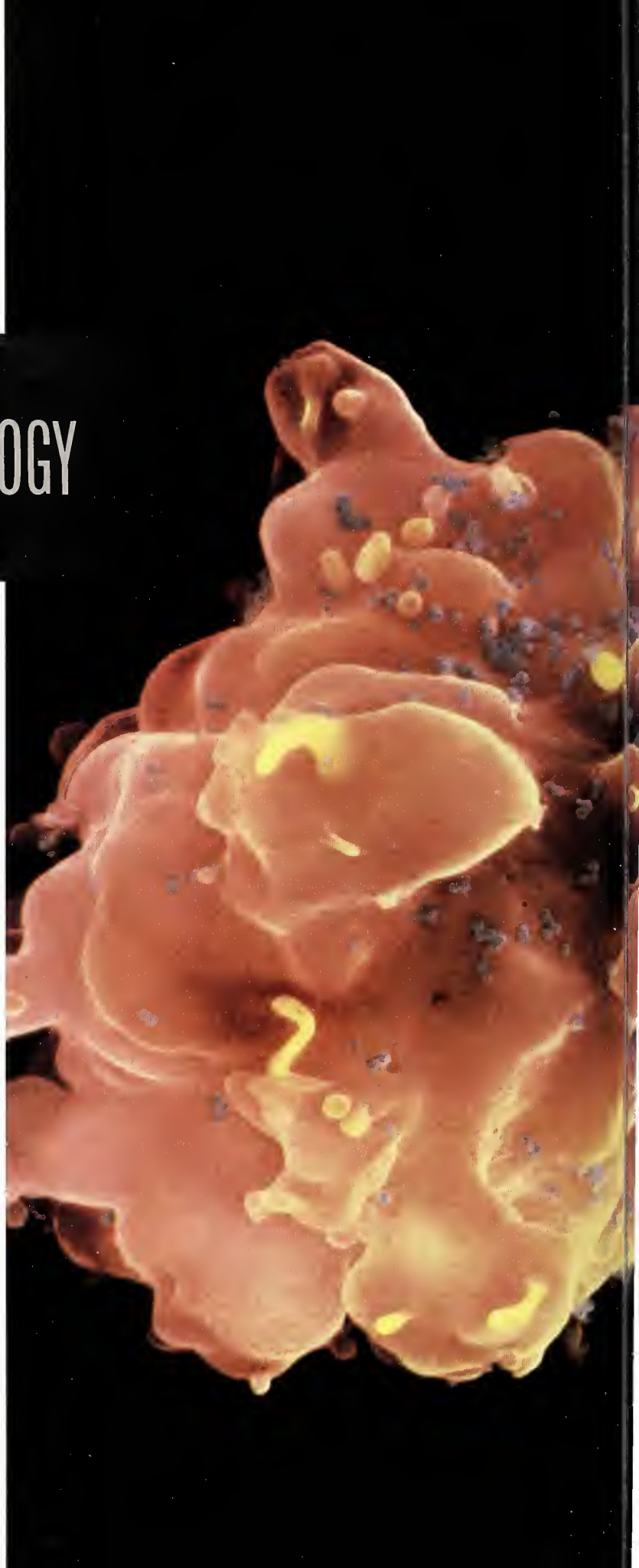
Knowledge of the immune system is essential to virtually every endeavor in modern medical science. Within the past two decades, scientists have accumulated an impressive amount of new information about the properties, functions, and regulatory controls of components of the immune system. Yet each discovery provokes further questions and suggests numerous avenues for exploration.

Scientists have learned that both B cells and T cells are further differentiated into subsets of cells with specific functions. The intermediate steps of the differentiation process are mediated by various surface molecules, some of which are decreased or lost while others become distinguishing markers for mature cells. At NIAID, basic studies are aimed at elucidating precisely the molecular mechanisms of lymphocyte development and division.

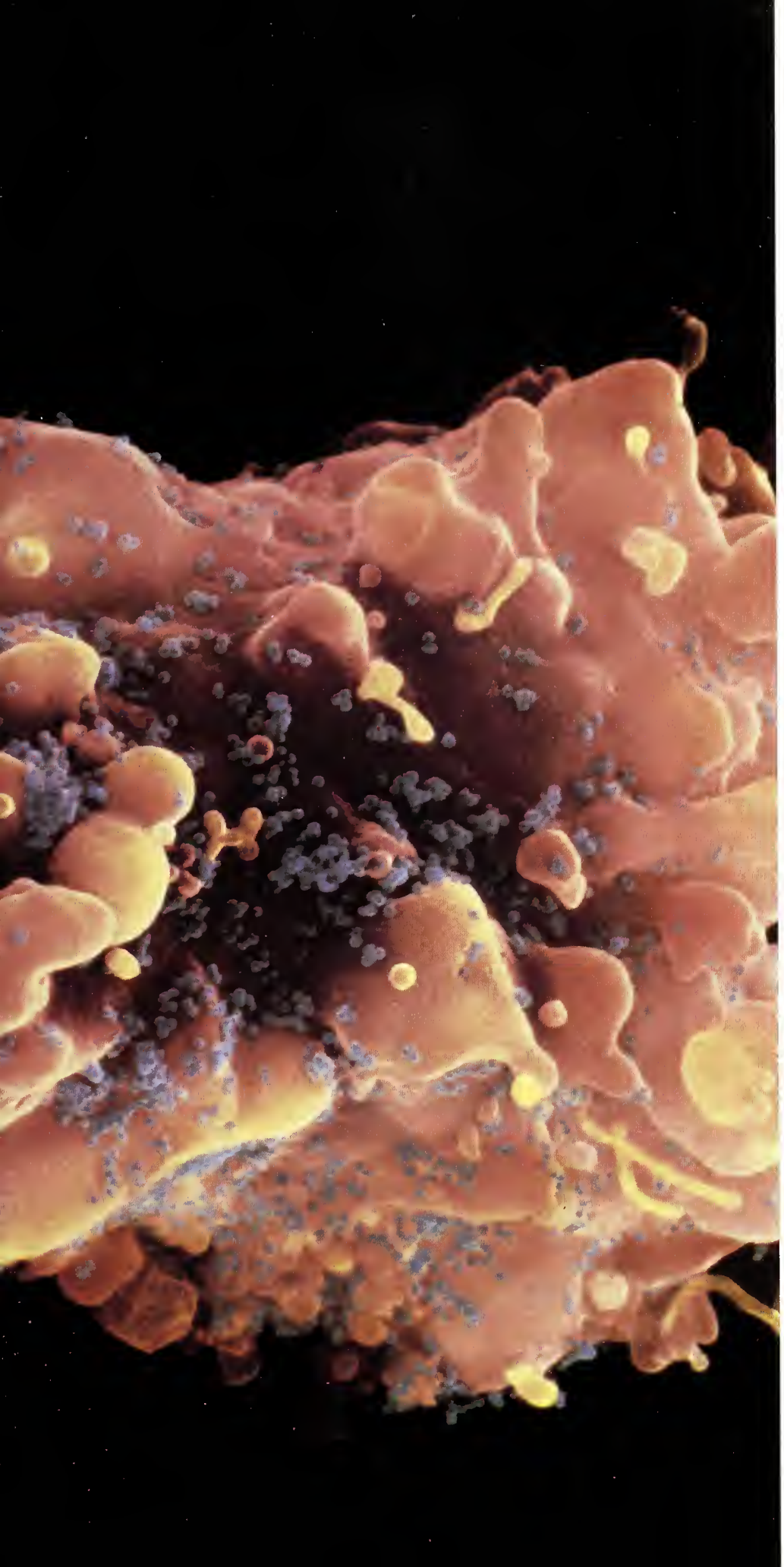
Study of B Lymphocytes

Prospects are especially bright for further rapid advances in knowledge about the structure and function of B lymphocytes. During differentiation, the precursors of B cells undergo a multitude of genetic rearrangements and changes. These changes give antibody-forming B cells the capacity to generate antibodies that will react with a seemingly infinite number of foreign antigens. It is estimated that a person can make billions of different antibodies in a lifetime.

In order to produce copious amounts of antibody to counter a specific antigen, B lymphocytes must proliferate and undergo further maturation. Lymphokines and B cell factors, other soluble substances that circulate in the body, regulate this process. NIAID investigators



T4 Helper T cell attacked by HIV (human immunodeficiency virus)



The Immune System: How It Operates

The immune system of the body is an elaborate and dynamic network of organs, cells, and substances whose proper functioning is essential to health. When the system operates normally, *lymphocytes* with a variety of specific functions constantly monitor the body for the presence of *antigens*, molecules that are present on abnormal or foreign substances. The lymphocytes collaborate to generate a vigorous, appropriate response. Lymphocytes derive from a common stem cell that is formed in the bone marrow. Lymphocytes differentiate in the bone marrow and in lymphoid organs such as the thymus. B lymphocytes, which mature in the bone marrow, provide an immune response by producing *antibodies*, also known as immunoglobulins, which are disease-fighting proteins that circulate through the body and neutralize or attack foreign substances. T lymphocytes, which mature in the thymus, are involved in cell-mediated immunity. "Helper" T cells regulate the delicate balance of the immune response and also play an essential part in antibody production. Activated helper T cells secrete *lymphokines*, soluble substances that circulate in the body and act as the alarm bells of the immune system. The lymphokines, which include interleukins, interferons, and other substances, help to mobilize and coordinate other cells in the immune response. *Monocyte-macrophages*, cells with numerous important functions, engulf foreign matter and present antigens to T cells in a form they can recognize and respond to. Another important element in the immune response is the *complement system*, which is made up of circulating proteins that are activated in sequence and directly attack bacteria and other invaders, and also contribute to inflammatory reactions. Other white blood cells—*neutrophils, eosinophils,* and *basophils*—act as the first line of cellular defense by rapidly mobilizing to digest the invaders.

are isolating and characterizing these factors and are identifying and cloning their genes.

They are also cultivating B lymphocyte precursors in the laboratory in order to analyze the gene rearrangements that determine specificity of responsiveness to an antigen. With this information in hand, it may be possible to provide genes that are missing or eliminate those that are undesirable. Such genetic intervention might be employed in the prevention and treatment of numerous diseases involving B cell dysfunction. These include a number of immunodeficiency diseases that manifest themselves in early childhood by repeated or chronic infection with a variety of bacteria and viruses and frequently result in neurologic damage or death.

Study of T Lymphocytes

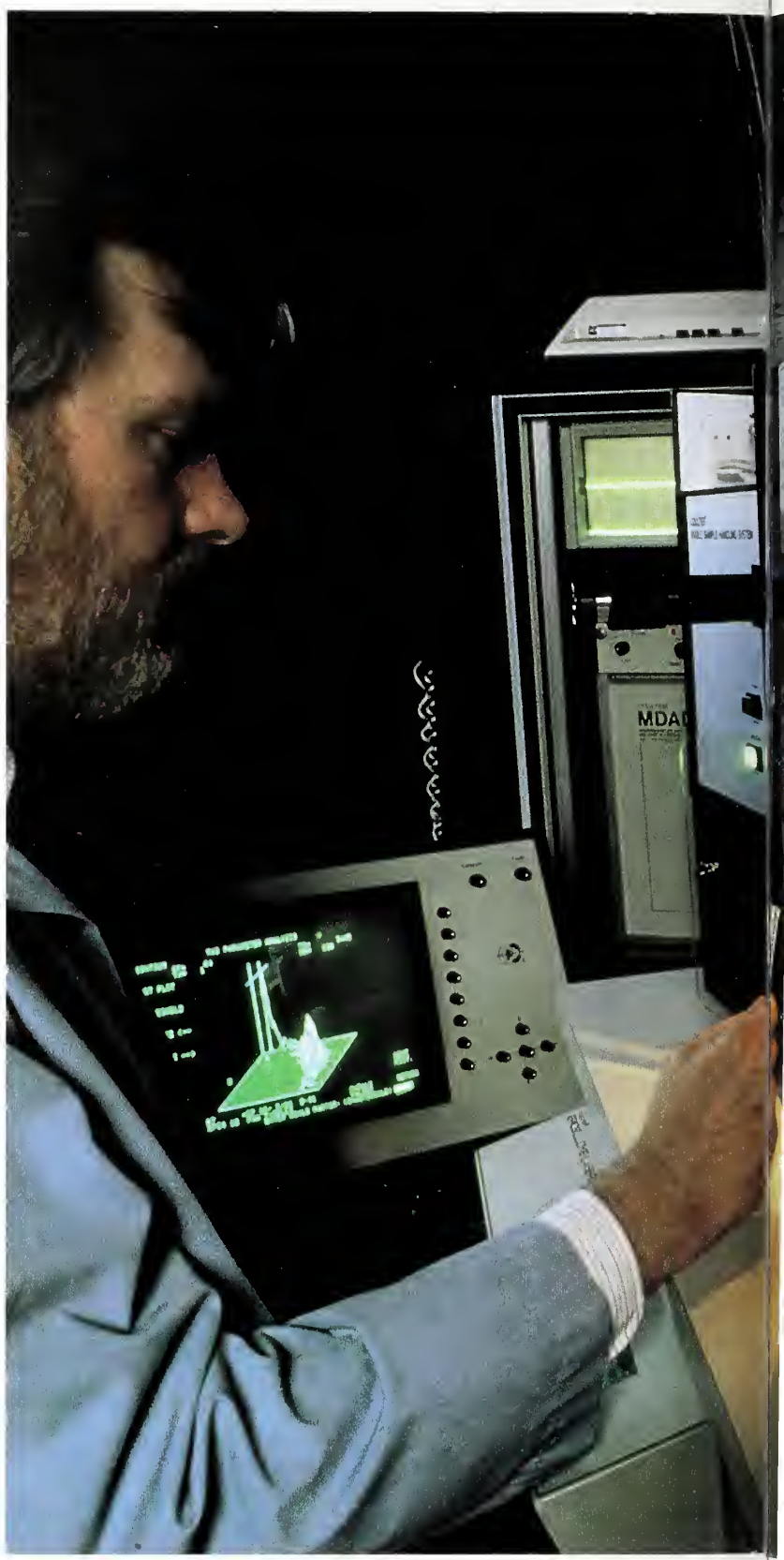
Intensive research on the interaction that occurs between T lymphocytes and monocyte-macrophage (antigen-presenting) cells is being conducted at NIAID. Scientists have identified specialized receptor molecules borne on the surface of helper and cytotoxic T cells and are attempting to learn more about how they participate in antigen recognition. The need for this information has become particularly urgent with the advent of AIDS (acquired immunodeficiency syndrome), which is caused by a virus with a propensity for attacking the T helper cell.

Increased understanding of the differing responses of developing and mature T cells to "self" and "non-self" antigens could provide important clues to the generation of autoimmune diseases.

Autoimmune Diseases

Systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and other diseases are considered *autoimmune* diseases. They occur when the immune system produces autoantibodies that launch an attack on the body's own normal cells, and specifically the nuclear components of cells. Although the precise causes of these diseases are still unknown, scientists theorize that they involve genetic predisposition, challenge by certain viruses, or exposure to certain environmental factors.

A number of researchers are investigating the relationship of these factors to a genetic component of the



The fluorescence-activated cell sorter (FACS), an invaluable tool of research in basic and clinical immunology, is used to isolate cellular components of the immune system for study, facilitate diagnosis of immune system diseases, and monitor therapy. The FACS measures quantitative and qualitative differences in surface antigens of mature and developing lymphocytes according to the amount of fluorescent dye that binds to each cell. It measures cell distribution according to fluorescence or size and separates cells by electrostatically charging them with a laser beam. The FACS is coupled to a computer that stores, manipulates, and displays data.


COHERENT

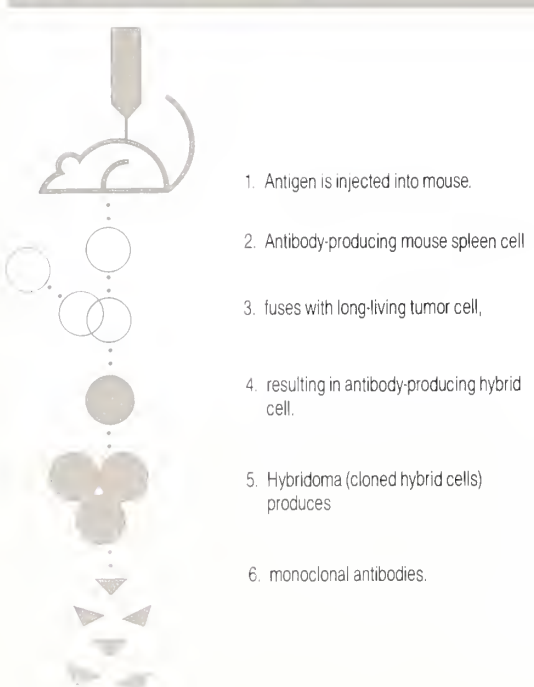
immune system known as the major histocompatibility complex (MHC). The MHC genetically determines the production of histocompatibility molecules, also known as HLA antigens. These are cell surface molecules that are used as markers by T lymphocytes to recognize foreign antigens on the surface of the body's cells. HLA antigens are unique to each individual. They determine a person's predisposition to autoimmune disorders as well as compatibility for organ transplants.

Immunology and Transplants

Closely linked to the study of autoimmune disease is the search for ways to improve success in organ and bone marrow transplants. The use of the drug cyclosporine to suppress normal immune responses to foreign tissue and thus prevent tissue graft rejection has been dramatically successful in many patients. Chances of transplant rejection can also be minimized by matching as closely as possible HLA antigens of organ donors and recipients. While neither approach is totally successful, and both have disadvantages, there is heightened public interest and demand for wider use of tissue transplants as life-saving measures.

NIAID is giving increasing emphasis to basic and applied research in transplantation immunobiology. Through molecular genetics, rapid strides have been made in determining the structure and function of the human HLA antigens that act as "self" markers on body cells. NIAID is supporting studies of lymphokines that are involved in the rejection process, as well as clinical studies using total lymphoid irradiation, drugs, and monoclonal antibodies to suppress immune responses.

Producing Monoclonal Antibodies



Intramural scientist Ronald Schwartz, M.D., Ph.D., uses a high performance liquid chromatographer to analyze and purify proteins, lipids and other substances.

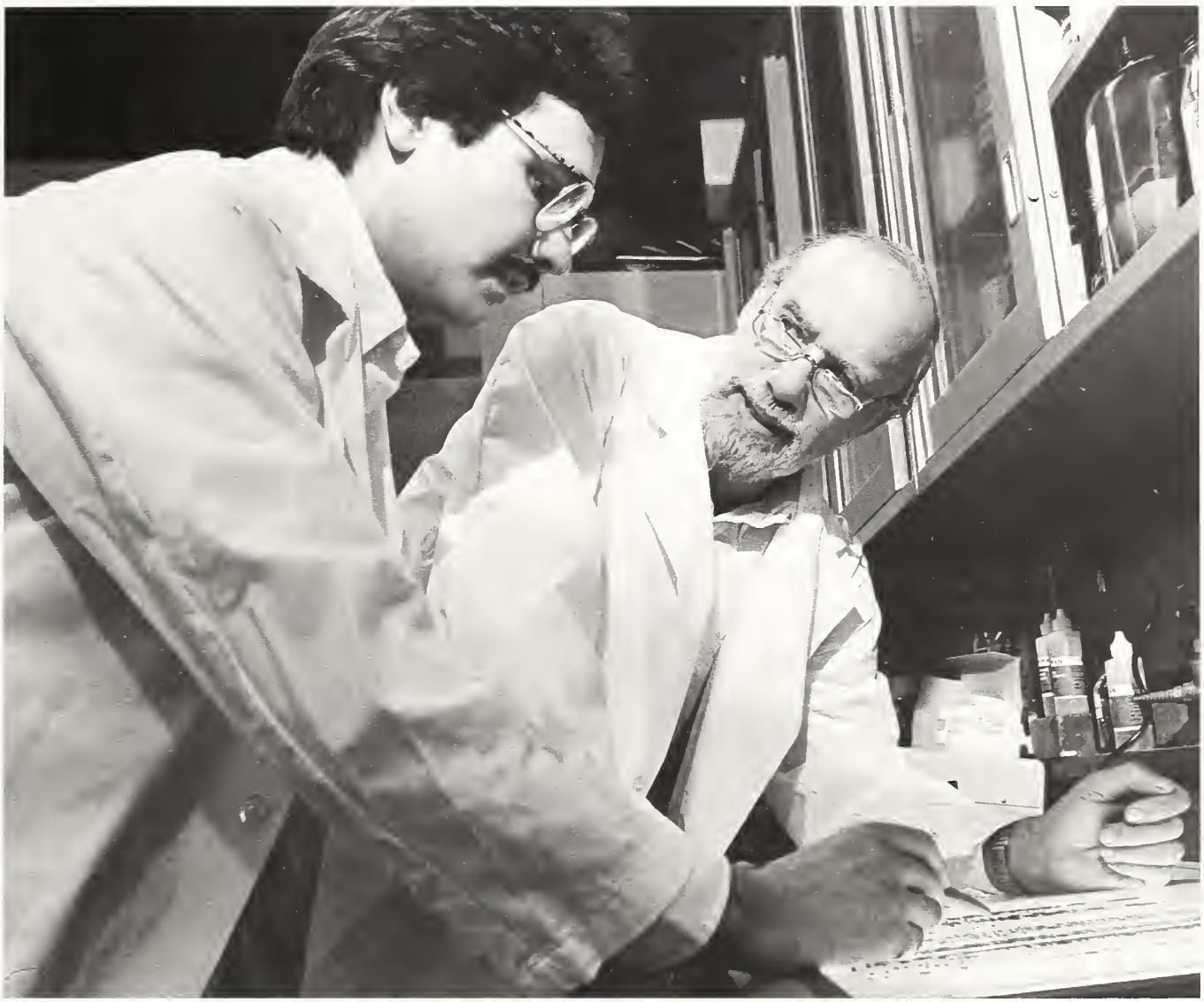
A monoclonal antibody made from a mouse hybridoma was licensed in 1986 for treating acute episodes of rejection following kidney transplants. Called OKT3, it temporarily halts the patient's T cell functions by reacting with the T3-antigen recognition structure. However, the treatment carries some hazards: because OKT3 is a mouse protein, it elicits an immune response in patients that can sometimes lead to a severe allergic reaction. Also, OKT3 interferes with normal as well as pathologic processes. These disadvantages give increased impetus to scientists' efforts to make human monoclonal antibodies.

Bone marrow transplantation, a transfer of stem cells taken from the bone marrow of a donor, is used extensively to treat children with congenital immunodeficiency diseases, as well as adults who are immunosuppressed as a result of cancer chemotherapy. A major hazard of this procedure is the development of graft-versus-host disease (GVHD). The symptoms of GVHD, which can be chronic and severely debilitating and can end in death, result from an attack on the patient that is mounted by certain T cells that are in the donor marrow. To counter this problem, NIAID is supporting clinical trials using specific monoclonal antibodies that cleanse T cells from the bone marrow.

Immunoregulatory Studies

Patients with such inflammatory vascular diseases as Wegener's granulomatosis, lymphomatoid granulomatosis, and polyarteritis nodosa have benefitted greatly from NIAID research on regulation of the immune system. Before the introduction of treatment regimens developed at NIAID, many of these patients died within a short time. The majority of those with Wegener's granulomatosis, for example, died within one year; now 93 percent of those treated with a combination of drugs experience complete remission.

Research on vasculitic diseases has, in turn, contributed to present knowledge of immunoregulation and has suggested new lines of research on other immune system diseases.



At Albert Einstein College of Medicine, Bronx, N.Y., Matthew D. Scharff, M.D., NIAID grantee for a number of years, and Ronald A. DePinho, M.D., holder of an NIAID Physician Scientist Award, are manipulating the structure of monoclonal antibodies. Their work draws heavily on the present knowledge of immunoglobulin genes and how they change when antibody-forming cells differentiate during the normal immune response. They are identifying rare hybridoma clones that undergo rearrangements, deletions, or somatic mutations in their immunoglobulin genes. Their goal is to produce monoclonal antibodies that will be more effective for particular tasks such as neutralizing toxins, protecting against infectious agents, or targeting tumors.

Biotechnology

New technologies have revolutionized immunology and promise an ever-increasing capacity to regulate more precisely normal and disordered immune responses.

Molecular genetics is the study of the molecules DNA (which carries the substance of heredity) and RNA (which chiefly is involved in protein synthesis). Genes, segments of DNA molecules that contain the codes for specific functions, can be isolated, spliced with DNA segments from other sources, and replicated or "cloned" by inserting them into cells.

Cultivation of cell lines of identical, *cloned lymphocytes* enables researchers to examine the structure of genes and proteins involved in antigen recognition, cell differentiation and life cycle, and events that lead to cell activation and proliferation. These studies are conducted on normal cells as well as those altered by the researchers in order to study certain characteristics.

Monoclonal antibodies are pure, highly specific antibodies produced in the laboratory. Hybridomas, cells made by fusing antibody-producing cells with long-living tumor cells, will produce unlimited quantities of identical antibodies against an antigen with which an experimental animal has been immunized. Because these monoclonal antibodies can be targeted to identify specific cells or substances in the body, they have the potential for numerous uses in medicine and in scientific research. Most of the monoclonal antibodies in current use are derived from mouse cells.

ALLERGY AND ASTHMA

Allergies and asthma are among the nation's most common and expensive health problems, accounting for one out of every nine visits by patients to physicians. At least 40 million people suffer from allergies to one or more substances and 15 million have asthma. These illnesses can be very debilitating and, particularly in the case of asthma, can cause death. They are costly not only in terms of medical care but in time lost from work, activity restriction, and emotional strain.

NIAID conducts and supports a variety of studies on the causes, pathogenesis, prevention, and treatment of allergic diseases and asthma. Research is conducted in the Institute's Bethesda laboratories and at the NIH Clinical Center, and at a large number of universities and medical centers.

Allergy

Allergy is a disorder of the immune system characterized by hypersensitivity (harmful, increased reaction) to specific substances. Probably the single most important discovery opening the way for intensive research on allergy was the identification by NIAID grantees of the IgE antibody as the factor responsible for immediate hypersensitivity in allergic diseases.

The antibodies that play such a critical role in normal immune response (see previous section) belong to five major classes of *immunoglobulins*—IgA, IgD, IgE, IgG, and IgM. Each has a different immunologic task. In most people IgE is present in very small amounts and functions only in helping to fend off invasions from parasitic worms. In susceptible persons, however, IgE is produced in abundance as a reaction to an *allergen* such as pollen, dust, or mold. IgE antibodies coat the surfaces of *mast cells*, which are most heavily concentrated in the respiratory and gastrointestinal tracts and the skin, and *basophils*, found in the blood. Each mast cell contains, in secretory granules, powerful chemical mediators such as histamine. A subsequent encounter with the same allergen triggers the release of the mediators which, in turn, contribute to the allergic reaction.

This elaborate process of "degranulation" is being studied in detail by NIAID grantees and intramural scientists. They have identified the interaction of the IgE molecule and the antigen molecule, the sequence of events that modifies the structure of the mast cell's outer membrane, and the process by which the granules fuse with the membrane and discharge the chemical mediators.

These investigators and others have built on this foundation to elucidate further the mechanisms of the IgE antibody response and have sought various means of suppressing the antibody formation. Another research avenue is the development of inhibitors for some of the key enzymes involved in the process of mediator release.

The exact effects of each chemical mediator have yet to be determined. Histamine is known to cause itching, constriction of smooth muscle in the bronchial tubes, and leakiness of blood vessels. The prostaglandins and the leukotrienes, two other groups of chemical mediators that have roles in allergy, are synthesized in mast cells as well as in several kinds of white blood cells. The leukotrienes are especially potent constrictors of the smallest airways of the bronchial tree.

Asthma

Asthma is a chronic but reversible obstruction of the airways, specifically the bronchi and bronchioles that carry air from the windpipe into the lungs. When the airways narrow, the patient experiences coughing, wheezing, and difficulty in breathing.

Numerous substances and events can provoke asthma in a susceptible person: allergens, infectious agents such as viruses or bacteria, lung irritants, cold air, exercise, emotional stress, sulfites, aspirin, or beta blockers.

Any of these factors can cause the bands of smooth muscle in the walls of the bronchial tubes to contract and go into spasm. The airways become inflamed and the mucous membranes that line the tubes swell, increasing production of mucus.

Depending on the degree of airway obstruction, asthma patients can be normal or near death. In fact, some 4,000 Americans die each year of asthma. Most deaths occur in persons over 50 years old, but asthmatic children under 9 are also at increased risk. Recently, despite advances in treatment, deaths from asthma have increased throughout the world. NIAID has initiated several programs to counter the recent sharp rise in pediatric asthma deaths in the United States, especially among inner-city children.

Treatment for Allergy and Asthma

One of the best methods for treating asthma and allergic diseases is the careful management of the environment to avoid the various substances and factors that trigger reactions. Asthmatic children in particular may be instructed in special exercises and techniques for self-management. In addition, physicians and other health professionals can provide emotional support for all family members.

Dust mites are the major source of house dust allergens.

Effective drugs are now available to either prevent or treat these conditions. New, improved antihistamines for allergies have been developed. For asthma, there are several alternatives: chromoglycate, which prevents mast cells from secreting mediators; methylxanthines, which halt certain enzymatic actions in smooth muscle cells and relax the muscles; beta-adrenergic (adrenalin-related) agonists, which dilate the airways; and corticosteroids, anti-inflammatory drugs that reduce swelling, mucus secretion, and the production of IgE. For some patients, the undesirable side effects often associated with systemic administration of steroids can be avoided by use of topical sprays containing locally active drug.

NIAID scientists and grantees are studying the pharmacologic control of mast cells and basophils with the hope of understanding the antiallergic mechanisms of the drugs currently in use and to uncover new therapeutic possibilities.

A number of scientists at NIAID and at grantee institutions are studying the allergic phenomenon known as late phase reaction (LPR), which is a second or delayed response to antigen exposure. LPR is an inflammatory reaction that has been observed in the skin, lung, and nose; it involves the migration of cells such as neutrophils, basophils, eosinophils, and mononuclear cells into the tissue. Intramural scientists found that the neutrophil, identified as the dominant cell in LPR, releases soluble factors that stimulate redegranulation of mast cells. This possibly contributes to bronchial hyperreactivity. Exposure to cold air, ozone, or infectious agents such as viruses can also contribute to this process.

Molecular and biochemical studies of the basophil and its mechanism of histamine release also promise new insights into the pathogenesis of asthma.

Pollen grain, one of many varieties.

Chronic Allergic Rhinitis

Chronic allergic rhinitis, a disorder of the nasal mucosa, affects millions of Americans. The symptoms—nasal congestion, watery discharge, sneezing, and sometimes conjunctival itching and bronchoconstriction—can progress to sinus disease, middle ear problems such as otitis media and temporary hearing loss, facial abnormalities resulting from chronic mouth breathing, and loss of ability to smell or filter pollutants and allergens from inhaled air. Research on nasal physiology is enabling physicians to differentiate among allergic, nonallergic, and infectious forms of rhinitis and to prescribe and evaluate appropriate therapy.

Mastocytosis

At the NIH Clinical Center, NIAID scientists are conducting a long-term study of mastocytosis, an unusual, severe disease caused by an overabundance of mast cells. The high concentration of mediators released by the mast cells results in bone pain, abdominal discomfort, nausea and vomiting, diarrhea, and skin lesions. These studies have led to improved diagnosis and treatment of mastocytosis and are also clarifying the normal function of mast cells.

Types of Allergic Reactions

		Mechanism	Examples
Type I	Immediate hypersensitivity or anaphylactic	IgE antibody on mast cell reacts with antigen resulting in release of mediators	Hay fever; allergic reaction to insect sting; allergic shock
Type II	Cytotoxic	IgG antibody reacts with cell membranes or with antigen associated with cell membrane	Reaction to transfusion of incompatible blood type
Type III	Arthus	Antigen and antibody bind together to form immune complexes that deposit in walls of blood vessels or kidneys	Serum sickness, some drug reactions
Type IV	Delayed hypersensitivity or cell-mediated	T cells interact directly with antigen	Poison ivy, graft rejection

Intramural Scientist Michael Kaliner, M.D., with a young patient.

Anaphylaxis

Anaphylaxis, an acute life-threatening immunologic condition, may be precipitated by exercise, foods, sulfites, insect stings, or other agents or events. The generation and release of chemical mediators, primarily those derived from mast cells, can affect the skin, the gastrointestinal tract, the upper and lower airways, and the cardiovascular system. Scientists at NIAID and at NIAID-supported medical centers are studying the mechanisms of anaphylactic reactions and evaluating medications and treatment regimens that may prevent or ameliorate them. Having established the efficacy of prophylactic venom immunotherapy in adults with histories of systemic reactions to insect stings, researchers are developing criteria for the duration of such therapy and are also studying venom allergy in children.

A Targeted National Program

To provide a focused and coordinated program of basic and clinical research specifically directed at improving the diagnosis, treatment, and prevention of asthma, allergies, and other immunologic diseases, NIAID sponsors several Centers for Interdisciplinary Research on Immunologic Diseases (CIRIDs) and a number of Asthma and Allergic Disease Centers (AADCs) throughout the country.

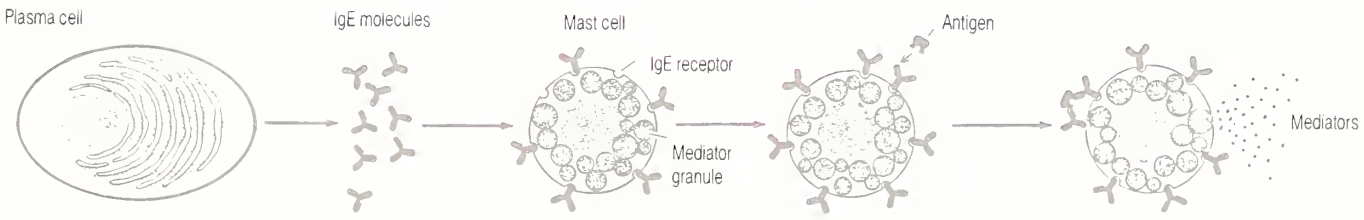
Located within a larger institution such as a university medical center, each center draws together a team of scientists who generally plan their research projects around a central theme of particular interest. A coordinated approach offers scientists from diverse disciplines access to sophisticated equipment for basic research and the opportunity for clinical studies in an appropriate complement of patients.

Research conducted by the units covers a broad spectrum. Studies pertinent to asthma and allergic diseases include: the use of various drugs for allergies and asthma; the role of various body cells in asthma; varying responses to release of histamine; interactions of eosinophils and lymphocytes; the role of complement in asthma and other diseases; drug reactions; the relationship between viruses and asthma; improved methods of diagnosing food allergies; and genetic determination of allergy and other autoimmune diseases.

Also contributing to knowledge of asthma and allergy are projects on prevalence, incidence, and recurrence of asthma; utilization of health care facilities; measurement of airborne allergens; and asthma care training for children.

Recruitment and training of fundamental and clinical investigators, continuing education of practicing medical professionals, and community education and outreach programs are other important functions of the CIRIDs and AADCs.

The Role of the Mast Cell in Allergic Reaction



IgE antibodies, produced by plasma cells in reaction to antigen (e.g., pollen), coat surface of mast cell. Subsequent encounter with antigen triggers release of mediators.

... that immunology and virology had reached a certain ... AIDS arrived on the scene. A few years ago, our ... technological expertise would have been insufficient to even ... syndrome, much less define precisely how the virus affects ... system or design therapies that could interfere with the disease ... restore the immune response. We still have much to learn, but we ... on a solid foundation.''

—Anthony S. Fauci, M.D.
Director, NIAID

AIDS

The Newest Challenge to Medical Science

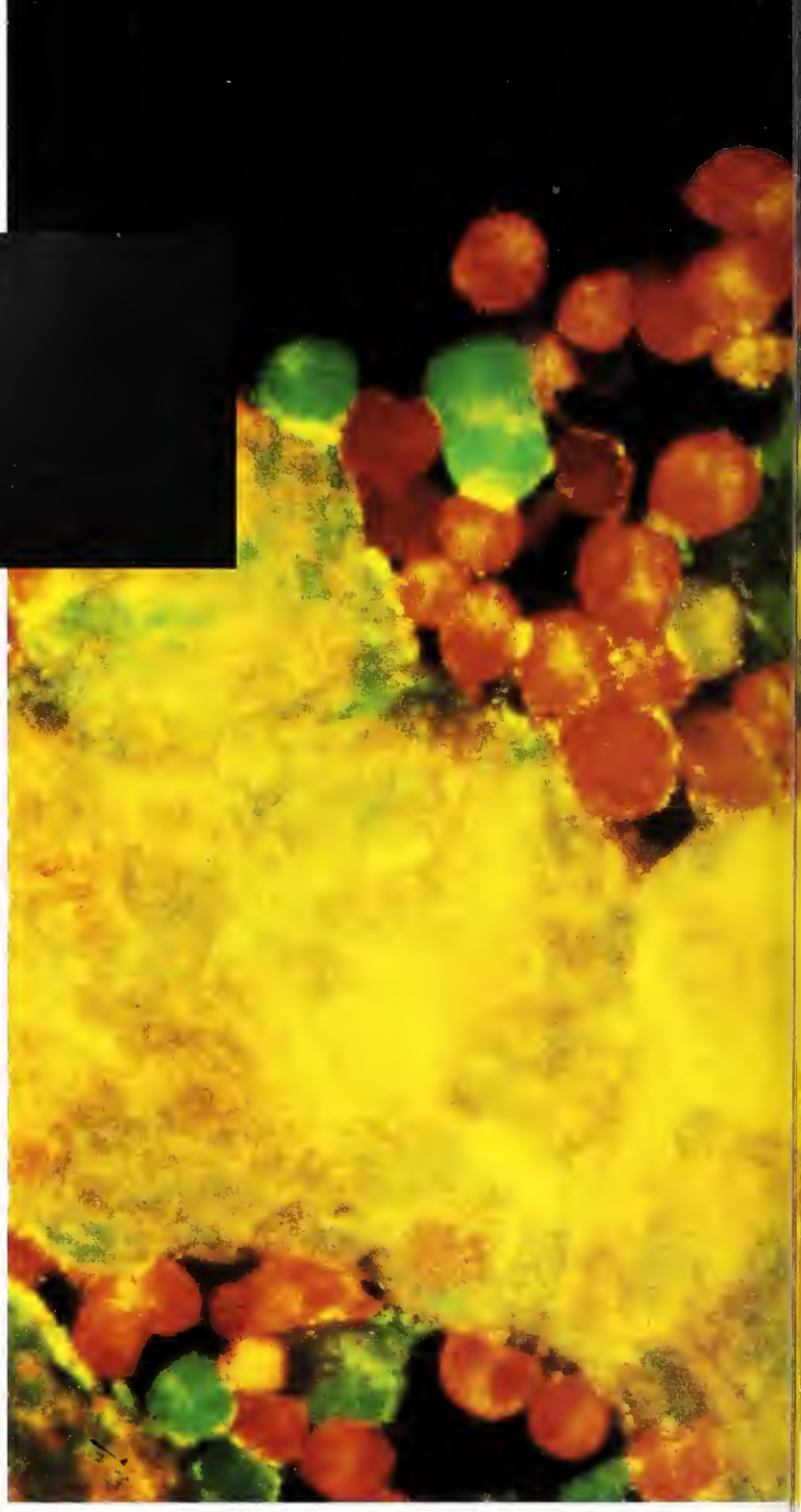
AIDS, or acquired immunodeficiency syndrome, is a devastating infectious disease of the immune system that reached alarming proportions within 5 years of its recognition in the United States in 1981. Following the discovery of the virus that causes AIDS, the Institute expanded and intensified its research efforts in pathogenesis, treatment, prevention, and epidemiology of the underlying infection and the opportunistic infections, cancers, and other conditions that characterize the disease. NIAID has become the lead component at NIH for coordinating, conducting, and supporting AIDS research in the United States.

Expanded knowledge of the immune system, acquired chiefly during the past two decades, combined with recent advances in virology and amplified by technological innovations, has offered the opportunity for a multifaceted and simultaneous exploration of many scientific questions about this disease.

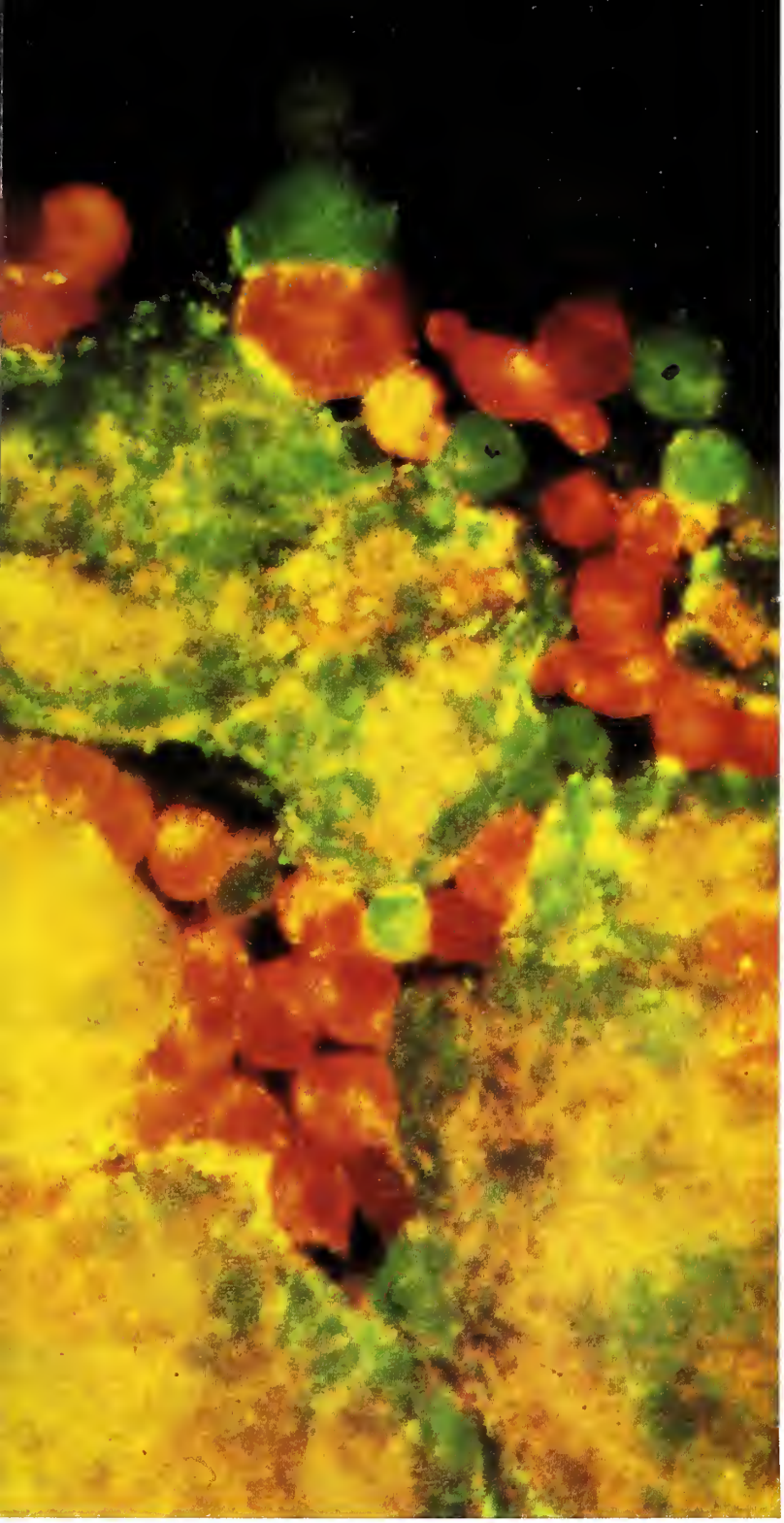
NIAID'S AIDS Research Priorities

NIAID scientists are studying the molecular biology of HIV in an effort to determine its characteristics and genetic structure. The immunopathogenesis of AIDS—the process by which HIV destroys the body's immune system—is only partially understood. Much needs to be learned about interactions between the virus and various target cells, about antibody and cell-mediated immune responses to the virus, and about effects of the virus on the immune system as a whole.

NIAID particularly emphasizes development of AIDS therapies, including both antiviral treatments and reconstitution of the immune system. Vaccine research involves work with other retroviruses as well as HIV. Studies of incidence and prevalence patterns of the disease among various populations and subgroups continue to furnish vital information about transmission and the possible role of cofactors in AIDS. In addition to conducting and supporting research in all of these areas, NIAID sponsors workshops on AIDS for physicians, other health professionals, and the general public.



Cells (red) infected with recombinant vaccinia virus containing envelope gene of AIDS virus are cultured with uninfected cells (green). The AIDS viral envelope protein causes cells to fuse, producing multinucleate giant cells (orange/green), leading to cell death.



What is AIDS?

AIDS is caused by a virus called HIV (human immunodeficiency virus). A sexually transmitted, blood-borne virus, HIV attacks and weakens the immune system, causing vulnerability to certain types of cancer and to various "opportunistic" infections caused by other viruses, parasites, fungi, and bacteria. These infections can usually be overcome by a healthy immune system but are frequently the cause of death in AIDS patients. Neurologic disease due to direct infection of the brain with HIV is also common in AIDS patients.

Basic Research on the AIDS Virus

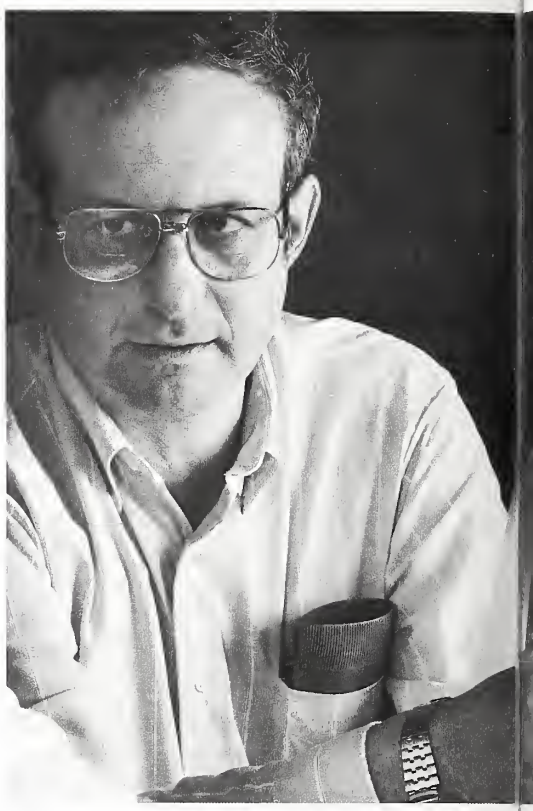
Scientists at NIAID were among the first to describe the precise immune defect that occurs in AIDS patients. They found that HIV has a propensity for attacking and destroying the subset of T lymphocytes known as T4 or helper/inducer cells. These cells, which are responsible for orchestrating virtually every function of the human immune system, express on their cell surfaces a protein molecule known as CD4. A number of other cells, including monocyte-macrophages, white blood cells that perform several vital immune functions, also express the CD4 molecule. In the immunopathogenesis of AIDS, CD4, which mediates cell-cell interactions, acts as a receptor that binds HIV to the cell and allows it to penetrate and enter the cell.

NIAID scientists have developed a CD4 T cell line that is easily infected by HIV. While most of the cells are killed by the virus, some survive and latently harbor virus. These latently infected cells can be induced to produce quantities of HIV by coinfecting them with a number of other organisms or their components. NIAID researchers have also developed an immature monocyte cell line that is a chronic, low-level producer of HIV. Cellular signals that might occur during a normal immune response are able to induce HIV replication in these cells. Scientists speculate that infected, asymptomatic persons harbor HIV and then convert to full-blown AIDS following exposure to other infectious agents—such as bacteria, fungi, or different viruses—that challenge the immune system.

Scientists are attempting to understand the pathogenesis of a common neurological complication in patients with AIDS—encephalopathy with progressive dementia. Recognized opportunistic infections of the nervous system account for only a small percentage of these cases. Using immunohistochemistry coupled with *in situ* hybridization techniques and electron microscopy, NIAID researchers showed in a small group of AIDS patients that mononucleated and multinucleated macrophages were the major cell types synthesizing HIV in the brain. The investigators postulate that these cells may arise from HIV-infected peripheral blood monocytes that traverse the blood-brain barrier and differentiate into giant cells in the brain.

Treatment Approaches

Techniques of molecular biology provide the key to information about HIV that is essential for devising innovative, targeted approaches to the treatment of AIDS. Distinctive in its complexity, the virus has been shown to contain novel genes that apparently control or influence its replication. Detailed analysis of the structure and functions controlled by specific genes is providing the rationale for designing drugs that might interrupt the life cycle of the virus and inhibit its replication.



Anthony S. Fauci, M.D., NIAID Director, conducts rounds with H. Clifford Lane, M.D., and Randi Leavitt, M.D.

A number of antiviral therapies are aimed at inhibiting reverse transcriptase, the enzyme that is essential for the virus to copy its genetic material (RNA) into a form that can be incorporated into the host cell's genetic material (DNA). The virus cannot replicate without using the cell's genetic machinery. Some of the initially most promising agents have been nucleoside analogs, drugs that interfere with DNA synthesis.

Immunomodulators, substances that influence specific immune functions or modify one or more components of the immunoregulatory network, have clear potential for the treatment of AIDS. Also known as biological response modifiers, they include lymphokines and monoclonal antibodies. NIAID scientists believe that research may show that the most effective treatment for AIDS patients will employ a combination of antiviral and immunoregulatory agents, as well as drugs specific for the patient's opportunistic disease or cancer.

In studies of identical twins, NIAID scientists have demonstrated that it may be possible to reconstitute the immune system of a person with AIDS by combining therapies—using antiviral drugs and transplanting bone marrow and lymphocytes from the patient's healthy twin. Though feasible at present only in identical twins, the technique warrants further study.

June Kwon-Chung, Ph.D., fungal geneticist, searches for mutants of *Candida albicans*, a common cause of infection in AIDS patients.

Intramural scientist Malcolm Martin, M.D., determines the nucleotide sequence for HIV envelope (outer protein coat).

Retroviruses

HIV, the virus that causes AIDS, is a retrovirus. A retrovirus carries its genetic information in the form of RNA rather than DNA. When it infects a human cell, the RNA is transcribed into DNA by the viral enzyme, reverse transcriptase. The viral DNA is then permanently incorporated into the genetic structure of the infected cell, which is instructed to manufacture new viruses.

Thomas C. Quinn, M.D., links clinical medicine, basic research, and epidemiology in his studies of AIDS and other sexually transmitted diseases.

AIDS Clinical Trials Program

To speed the evaluation of promising AIDS therapies, NIAID has enlisted many outstanding investigators to conduct clinical trials of experimental drugs in persons infected with HIV. Linked in a nationwide network of AIDS Clinical Trials Units at a number of U.S. medical centers, the researchers collaborate in the design of protocols for testing specific therapies in various patient groups and share their findings rapidly by way of a computerized database system.

Vaccine Research

Many questions influence progress in the search for the ultimate weapon against AIDS—a vaccine to prevent infection. Understanding the body's immune response to HIV and why people vary in their immune susceptibility to infection is crucial to this effort. The complexity of the virus, the existence of multiple HIV strains, and the lack of adequate animal models for testing candidate vaccines are serious obstacles. NIAID is addressing all of these questions through basic and clinical research.

Research conducted by NIAID scientists contributed to the development of the first two experimental AIDS vaccines approved for testing in humans in the United States. In October 1987, NIAID intramural scientists initiated a clinical trial of a recombinant vaccine consisting of HIV envelope glycoprotein; this vaccine is also being tested in volunteers at NIAID's six university-based Vaccine Evaluation Units.

To foster additional, innovative approaches to AIDS vaccine development, NIAID funds several National Cooperative Vaccine Development Groups, composed of research teams drawn from academic institutions, industry, and government.

The Epidemiology of AIDS

Closely tied to basic and clinical research on AIDS are the Institute's epidemiology studies. A multicenter prospective study, established at the beginning of the AIDS epidemic, has provided invaluable information on the natural history of the disease in homosexual and bisexual males. The roles of specific sexual behaviors in transmission have been conclusively demonstrated, and the centers are studying the role of coinfection with other organisms such as hepatitis B in pathogenesis.

NIAID is also conducting studies of disease incidence in Central Africa, where AIDS is quite prevalent, and in collaboration with the Pan American Health Organization is exploring the epidemiology and natural history of AIDS in the Caribbean and other areas of high incidence.

VACCINES

New Horizons in Disease Prevention

Vaccines are history's most successful public health tools. Through immunization smallpox has been eradicated from the globe. Universal immunization with the vaccines that are available today could provide worldwide control of numerous diseases and their complications: influenza, pneumococcal pneumonia, hepatitis B, meningitis, and other diseases for which childhood immunizations are given routinely in developed countries. The list is impressive and growing.

Yet the list of diseases for which there are still no vaccines is even longer, and the need to make many existing vaccines safer, cheaper, and more effective is great.

NIAID is the fountainhead of vaccine research and development within the Public Health Service. The Institute's broad research programs on all classes of infectious diseases and their causative agents, together with basic research on the immune system, have nourished a comprehensive, collaborative vaccine effort among scientists in government, industry and academic institutions.

Opportunities are burgeoning for the development of new and improved vaccines for the entire spectrum of infectious agents—bacteria, viruses, fungi, and parasites. Recombinant DNA technology, the production of monoclonal antibodies by hybridomas, nucleic acid sequencing, and peptide synthesis have opened the way for producing refined or synthetic, highly specific immunogenic antigens that can be incorporated into vaccines. These advances, coupled with possibilities for manipulation of antibody and cellular immune responses, offer hope for the ultimate prevention of many diseases.

Pertussis

Until the 1950's, whooping cough, or pertussis, caused illness in 100,000 American children each year, resulting in 4,000 to 5,000 deaths and leaving many children with long-term neurologic injury. Widespread use of the pertussis vaccine has dramatically changed that. Today cases number 1,000 to 3,000 a year, with 5 to 20 deaths.

Recently, however, public confidence in the vaccine has eroded because of adverse reactions that in rare instances have led to permanent brain damage or death.

Replacement of the present vaccine, which is made of heat-killed, whole *Bordetella pertussis* bacteria, by a less toxic but equally effective product is a high priority of the NIAID. The Institute supports several different approaches to solving this problem.

Pinpointing the components of the pertussis organism that must be present to stimulate an immune response in humans and distinguishing those from components responsible for side effects are of paramount importance. These efforts have been hampered by the complexity of the bacterium and the lack of an animal model of the disease.

At NIAID's Rocky Mountain Laboratories in Hamilton, Montana, scientists are characterizing in detail the genetic and molecular structure of *B. pertussis* with the aim of defining which gene products are critical in the disease process. Having successfully cloned, or replicated, the pertussis toxin gene, they hope to remove the sites on the toxin molecule that are responsible for toxic activity. Their ultimate goal is development of a recombinant vaccine that would incorporate nontoxic, immunity-producing subunits of the pertussis bacteria.

In the meantime, acellular vaccines made from one or more major pertussis protein components offer considerable promise. Acellular vaccines, developed originally by research firms in Japan and used there for several years, have been evaluated in NIAID's Vaccine Evaluation Units, for safety and effectiveness in eliciting immune response. In a collaborative effort with Sweden, NIAID initiated the first controlled field trial of two Japanese acellular pertussis vaccines. Sweden is an ideal location for a large-scale efficacy trial because use of pertussis vaccine was discontinued there some years ago and whooping cough is now common.

How Vaccines Work

Most vaccines consist of an altered, weakened or killed form of a microorganism that is introduced into the body. Protein or carbohydrate components (antigens) of the microorganism stimulate the body's immune system to produce protective antibodies that are needed to prevent disease caused by that specific organism. After processing the antigens, a memory system is established that allows the immune system to recall which antibodies are needed to counter the organism if subsequent exposures occur. If antibody levels are sufficient, the individual will be protected against disease from "wild-type" or virulent forms of that particular organism. The safest vaccines contain only nonvirulent organisms or toxoids (detoxified toxins) that will provoke an immune response but will not cause harmful side effects.

An indispensable tool in rotavirus research is the electron microscope, which allows direct visualization of the site of antibody attachment to the virus particle.

A Vaccine for Meningitis

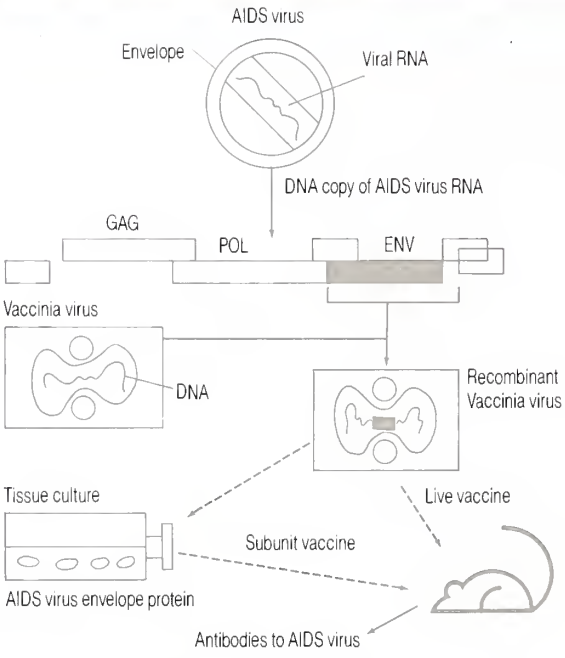
The bacterium *Haemophilus influenzae* type b (Hib) presents a different sort of research challenge. The Hib organism, which is the major cause of bacterial meningitis among American children and is responsible for several other life-threatening or severe illnesses, is coated with a polysaccharide shell, or capsule, known as PRP. Purified PRP is the antigenic constituent of a Hib vaccine that was licensed in 1985 for use in children over 2 years old.

PRP fails to induce an antibody response in infants and young children, the group most at risk for Hib infection. Presumably this is because, in the immature immune system, polysaccharides do not activate T helper cells, which signal B cells to produce antibodies. In order to convert PRP into a T cell activating antigen, scientists chemically bonded PRP to diphtheria toxoid. Compared to PRP, this "second-generation" conjugate vaccine was found to stimulate higher antibody levels; it is now licensed and recommended for routine use in children at 18 months and older.

Following extensive studies showing that the conjugate vaccine is more readily recognized by an infant's immature immune system, NIAID initiated a large-scale efficacy study of PRP-D in Alaskan Native infants. Eskimo, Aleut, and Indian infants are at very high risk of Hib infection, with rates many times those seen in non-Native populations. If the conjugate vaccine prevents meningitis and other Hib diseases in the Alaskan study and in another efficacy study in Finland, it will probably be licensed for use in infants and recommended worldwide for well-baby care.

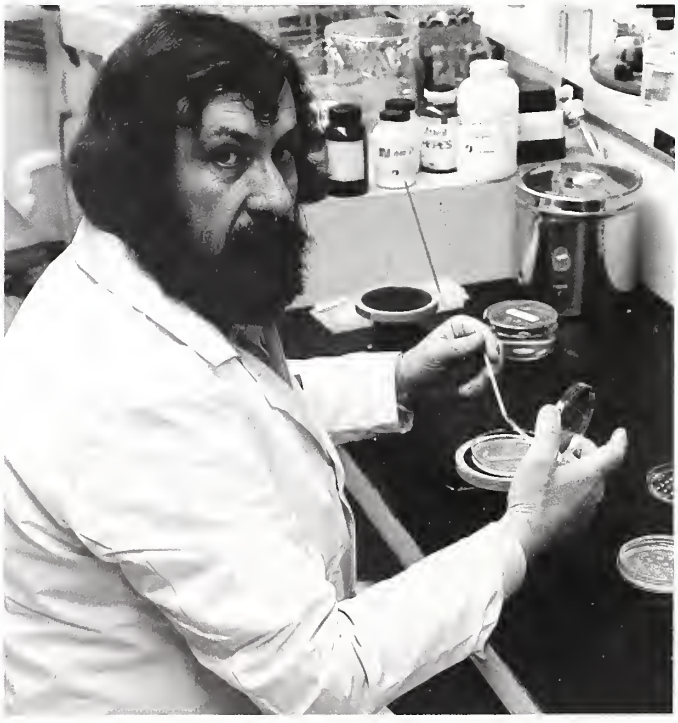
The Alaskan Hib vaccine study, which is a collaborative project with the Alaska Native Health Service, the Centers for Disease Control, and investigators at Harbor/UCLA, typifies NIAID's networking approach to vaccine research. Working from the keystone position, NIAID participates in all phases of development, from recognizing a specific need and formulating a concept or approach, through laboratory development of a new product, testing in animals, and the various stages of clinical trials before a vaccine can be licensed by the FDA.

Recombinant DNA Technology in the Production of an AIDS Vaccine



Hepatitis B

NIAID is supporting a number of efforts to develop hepatitis B vaccines using recombinant DNA techniques that avoid the use of material from human blood; they are genetically engineered by inserting genes from the virus into yeast, mammalian or insect cells and producing viral antigens which when incorporated into a vaccine can produce an immune response in the host.



At Rocky Mountain Laboratories, Jerry Keith, Ph.D., conducts genetic and molecular studies of pertussis bacteria.

Diarrhea

Worldwide, rotaviruses are the most important cause of severe diarrhea in infants and young children. Although the increased acceptance and use of oral rehydration has considerably reduced diarrhea mortality, development of a rotavirus vaccine continues to be a high priority.

Efforts have been spurred by recent, significant advances in rotavirus research. The ability now to grow human rotaviruses in tissue culture and the classification of several human rotaviruses by serotype are enabling scientists to analyze and specifically characterize human strains. "Reassortant" rotaviruses, constructed by combining specific genes from human and animal strains, are being evaluated as vaccine candidates.

One promising strategy involves use of an animal rotavirus strain that can infect humans and evoke cross-protective immunity without causing illness. NIAID investigators created such a vaccine using virus isolated from a rhesus monkey with diarrhea. The vaccine, which was shown to be both safe and immunogenic, is undergoing field trials in infants in the United States, Europe, and South America. Among the questions that are being addressed are the role of maternal antibody in modifying response among newborns and possible interference with response if the vaccine is administered along with poliovirus vaccine. NIAID also is supporting research on vaccines for other diarrheal diseases such as cholera and typhoid.

Accelerated Development of New Vaccines

NIAID has assumed major responsibility for the development of new and improved vaccines for diseases that present special risk for certain populations as well as diseases that are endemic to developing countries. In setting priorities for vaccine development, the Institute weighs expected health benefits, projected net costs, and feasibility given the current status of scientific knowledge about particular diseases and their causative agents.

The highest priorities have been assigned to research on new or improved vaccines to protect against these diseases:

— Whooping cough (pertussis)
— AIDS (acquired immunodeficiency syndrome)
— Meningitis caused by *Haemophilus influenzae* type b
— Croup and pneumonia in infants and children caused by respiratory syncytial virus
— Respiratory infections caused by pneumococcus
— Influenza
— Chickenpox (varicella)
— Diarrhea caused by rotaviruses, *Salmonella typhi*, shigella, and cholera
— Hepatitis B
— Malaria (*P. falciparum*)
— Gonorrhea
— Leprosy

Recombinant Vaccinia Vaccines

Commanding intense interest at NIAID for several years has been the creation of live recombinant vaccines by inserting genetic material from various disease-causing agents into the vaccinia (cowpox) virus. The remodeled virus retains the ability of the vaccinia virus to produce local infection when inoculated into the skin, and stimulates formation of antibodies against both vaccinia and the other agent.

NIAID scientists have produced and tested in animals vaccinia virus recombinants containing individual genes from viruses that cause a number of diseases, including hepatitis B, influenza, rabies, AIDS, and herpes simplex type 1. Recently, NIAID scientists have been encouraged by results from animal studies using such recombinant vaccines against respiratory syncytial virus, a frequent contributor to serious respiratory infections in children.

With a genome of 185,000 base pairs, the vaccinia virus has an unusually large capacity for the insertion of foreign genetic material. This fact has led to speculation that one recombinant vaccine could be used to immunize against multiple diseases. Such a vaccine, with its lower cost and ease of storage and administration, could dramatically improve disease prevention, particularly in developing countries.

Anti-Idiotype Antibodies: The Vaccines of the Future?

NIAID intramural scientists and grantees are exploring new ways of manufacturing vaccines in the future by using "anti-idiotype antibodies." This line of research is based on the theory that antibody production is controlled by a complex immune regulatory network. Specific antibodies (called idiotypes) that are produced in response to specific antigens can themselves act as antigens and elicit the formation of antibodies. These new antibodies, called anti-idiotypes, can act in turn as antigens and induce antibody formation. The process is repeated over and over.

In animal studies, injection of such "anti-idiotype antibodies" has produced protective immunity against various bacteria, viruses, and parasites. Such vaccines could offer a singular advantage in humans: no pathogenic material would be incorporated, thus avoiding harmful side effects. Vaccine manufacture could be enhanced in cases where a particular organism cannot be grown in sufficient quantities, is too toxic, or is nonimmunogenic when pure.

SEXUALLY TRANSMITTED DISEASES

Sexually transmitted diseases (STDs) have been known throughout the ages, but during the past 30 years they have become an increasing health problem in many parts of the world. The sharply rising incidence is attributed to changes in sexual behavior among persons of all ages, the increase in numbers of teenagers and young adults—those most at risk for STDs, the emergence of drug-resistant microbes, and improved diagnostic methods.

In many countries, including the United States, chlamydial infections, gonorrhea, genital herpes, and genital warts are at epidemic levels. These diseases can result in serious, sometimes fatal conditions, particularly for women and their newborn children. AIDS, a lethal new STD, has spread rapidly among certain high-risk populations—primarily male homosexuals and drug abusers in the United States and Western Europe—and now threatens sexually active heterosexuals as well.

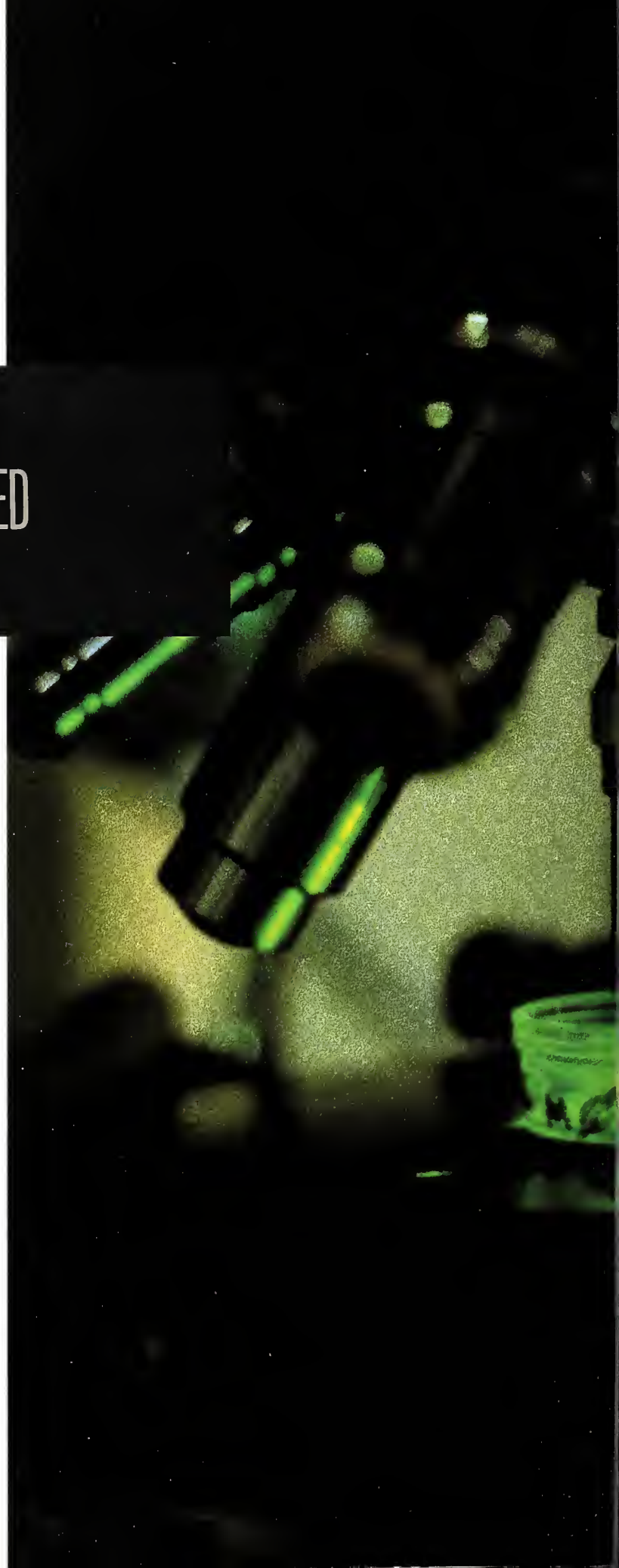
NIAID conducts and supports a vigorous program of basic and clinical research aimed at developing improved methods of preventing, diagnosing, and treating sexually transmitted diseases. Important components of this program are several large, multidisciplinary, university-based research units.

Some 20 different organisms are known to cause sexually transmitted diseases. NIAID is emphasizing research on those that cause the majority of infections and the most severe consequences.

Chlamydial Infections

Chlamydia is now recognized as the most common cause of STD. Because chlamydial infections are often symptomless, diagnosis may occur only after appearance of complications, such as infertility or ectopic pregnancy resulting from pelvic inflammatory disease. Conjunctivitis and pneumonia in newborn babies can result from chlamydial infections transmitted from mother to child. Repeated infections with chlamydia can result in blindness, a frequent problem in developing countries.

Chlamydia trachomatis, the bacterium that causes the infection, has a complex life cycle. Chlamydiae are intracellular organisms that attach to and enter cells and then convert to a different form. After 48 hours, some of the transformed organisms revert to an infectious form and rupture the infected cells. They invade other neighboring cells, causing more tissue destruction and an inflammatory discharge. The relationship between the organism and the host cell remains poorly understood.



Diagnostic tests employ immunofluorescence to detect virus-specific antibodies.

The pathogenic process by which chlamydiae establish latent infections and cause chronic inflammation in some individuals is also unclear. Using technologies such as recombinant DNA and monoclonal antibodies, NIAID scientists are attempting to learn more about the pathogenesis of chlamydial infections and the role of the immune response in eradicating or resisting infection.

Until recently, diagnosis of chlamydial infections was hampered because the bacterium is not easily grown in tissue culture. This hurdle was overcome with the development of a highly specific monoclonal antibody by NIAID-supported scientists in collaboration with researchers in private industry. The antibody, labeled with a fluorescent dye, was used to develop a rapid, accurate, and inexpensive diagnostic test for chlamydia. The technique, which is constantly being refined, requires little equipment and can be taught quickly, so it can be used easily in a physician's office. Routine use of this and similar rapid diagnostic tests would have a significant impact on health, as chlamydial infections respond well to treatment with antibiotics.

Gonorrhea

Gonorrhea, which is caused by a highly contagious bacterium, can result in complications that affect the heart, brain, or joints and can cause blindness in newborn babies. Incidence of the disease has increased in recent years, in part because some gonococcus strains have become resistant to penicillin and tetracycline, antibiotics that formerly killed the organism. In addition, new and more virulent gonococcal strains have appeared.

To develop an effective vaccine against gonorrhea, an important research objective of NIAID, scientists must overcome certain impediments. There is at present no animal model of the disease in which to test vaccine candidates. Furthermore, gonococci have great antigenic variation. Scientists at Rocky Mountain Laboratories have identified specialized genetic mechanisms that allow the bacteria to make innumerable different types of surface components, called pili, that are believed to be the mechanism of attachment to human cells. One way of preventing attachment and subsequent disease, the scientists believe, would be to develop a vaccine directed against the pili.

Genital Herpes

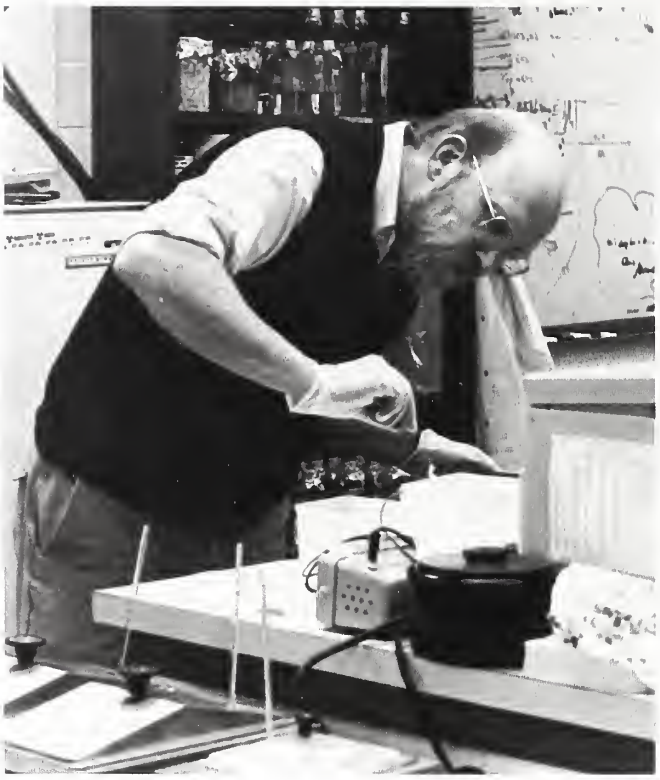
From blood tests of a sample of the general population, NIAID-supported scientists have estimated that 30 to 35 percent of Americans have been exposed to herpes simplex virus type 2 (HSV-2). Many of these persons report no signs of infection. There is now evidence that asymptomatic persons can infect their sexual partners, a fact that partially explains the rising numbers of persons who suffer from genital herpes infections.

Like all members of the herpesvirus group, HSV-2 never leaves the body following infection, and many people have recurrent outbreaks of disease.

Scientists at NIAID and elsewhere conducted the research that led to the licensing of acyclovir, the first oral antiviral drug proven to be helpful in managing genital herpes episodes and preventing recurrences. The drug produces few adverse reactions and no apparent toxicity. Although acyclovir is not a cure for genital herpes, it reduces viral "shedding," or production. Further studies have shown that long-term suppressive therapy carries minimal risk.

The most serious consequence of HSV-2 infection is transmission from mother to newborn child. NIAID has devoted much attention to the prevention of neonatal HSV-2 infections, which can result in brain damage or death. Several new, accurate, and rapid diagnostic tests are being developed to help detect active HSV-2 infection in the birth canal just prior to delivery. Such tests will help determine the necessity for a caesarean section to prevent herpes transmission to the baby. NIAID also supports a number of studies comparing the use of antiviral drugs in infected babies.

Using recombinant DNA techniques, NIAID scientists have developed a herpes vaccine that has been tested in animals. Eventually, they hope to produce a vaccine that is effective against both initial and latent genital herpes infections.



John Swanson, M.D., Rocky Mountain Laboratories, studies the genetic events that result in structural and antigenic differences among gonococcal pili.

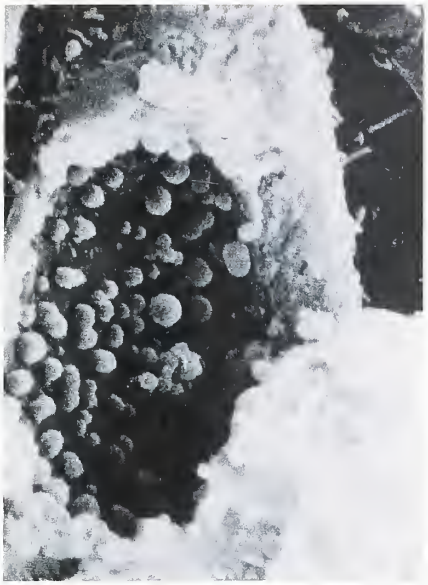
Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID), which occurs when disease-causing microorganisms migrate from the vagina and cervix into other reproductive organs, can result in infertility or ectopic pregnancy. The most frequent cause is infection with either chlamydiae or gonococci bacteria. Diagnosis is hard to pinpoint, and treatment choice is difficult due to the number of organisms that might cause the disease.

NIAID has demonstrated increased awareness of the need for studies of this condition by establishing several PID research units.

Diagnostic Techniques

Cultivation of the organism from the patient is the traditional and sometimes the only way to diagnose many diseases, but antigen or antibody tests offer another choice or can supplement these methods. Many rapid test kits now commercially available for the diagnosis of bacterial and viral infections from clinical specimens employ monoclonal antibodies (MoABs). As MoABs are antigen-specific, they can be designed to increase the sensitivity of the tests and are available in practically unlimited quantities. These tests include direct immunofluorescence and the enzyme-linked immunosorbent assay (ELISA). NIAID supports a number of studies aimed at improving these tests and developing other diagnostic approaches. *In situ* hybridization, a technique that is used increasingly in clinical research, involves using chemically or radioactively labeled strands of DNA as probes to locate matching strands in tissue samples.



Chlamydiae are released from a cultured, infected human cell after completion of intracellular growth cycle.

Hair-like pili seen on exterior surface of gonococci, facilitate attachment to host cells and promote infectivity of the bacteria

Scanning electron micrograph of syphilis spirochete, *T. pallidum*

Genital Warts

One of the most dangerous STDs for women is infection with human papillomavirus (HPV), which causes condylomata acuminata (genital warts) and has been associated with genital cancers. The paucity of current scientific knowledge about HPV has prompted NIAID to give HPV research a high priority.

At present, medical diagnosis is primarily limited to clinical evaluation, as the virus cannot be grown in tissue culture. It is possible, however, for researchers to distinguish among the various HPV types by using DNA probes to detect viral DNA in a lesion. NIAID-supported scientists are studying the various HPV types and their properties. Certain of the HPV types that appear in the human genital tract have been implicated in cervical cancer.

Genital warts are currently treated by destroying tissue, but virus can remain in surrounding tissue and warts can recur. NIAID is supporting clinical studies of several systemic therapies, used alone or in combination with topical treatment.

Syphilis

Syphilis, caused by the bacterium *Treponema pallidum*, is easily treated with antibiotics, but many infected people fail to recognize their illness and do not seek treatment. Untreated syphilis can result in four separate disease stages, each with different clinical symptoms, and can lead to mental disorders, blindness, and death. Syphilis transmitted to an unborn child can result in severe mental and physical problems.

For some time, syphilis diagnosis has depended on the physician's recognition of symptoms, blood tests, and microscopic identification of bacteria. NIAID grantees have overcome a major obstacle in syphilis research by developing techniques for growing the organism in the laboratory. New knowledge about the surface components of the bacteria and the body's immune response to them is being used to understand the course of the disease, improve diagnostic tests, and design vaccine approaches.

Numerous young investigators have benefitted from clinical and laboratory training with the renowned research team at the University of Washington's sexually transmitted diseases unit.

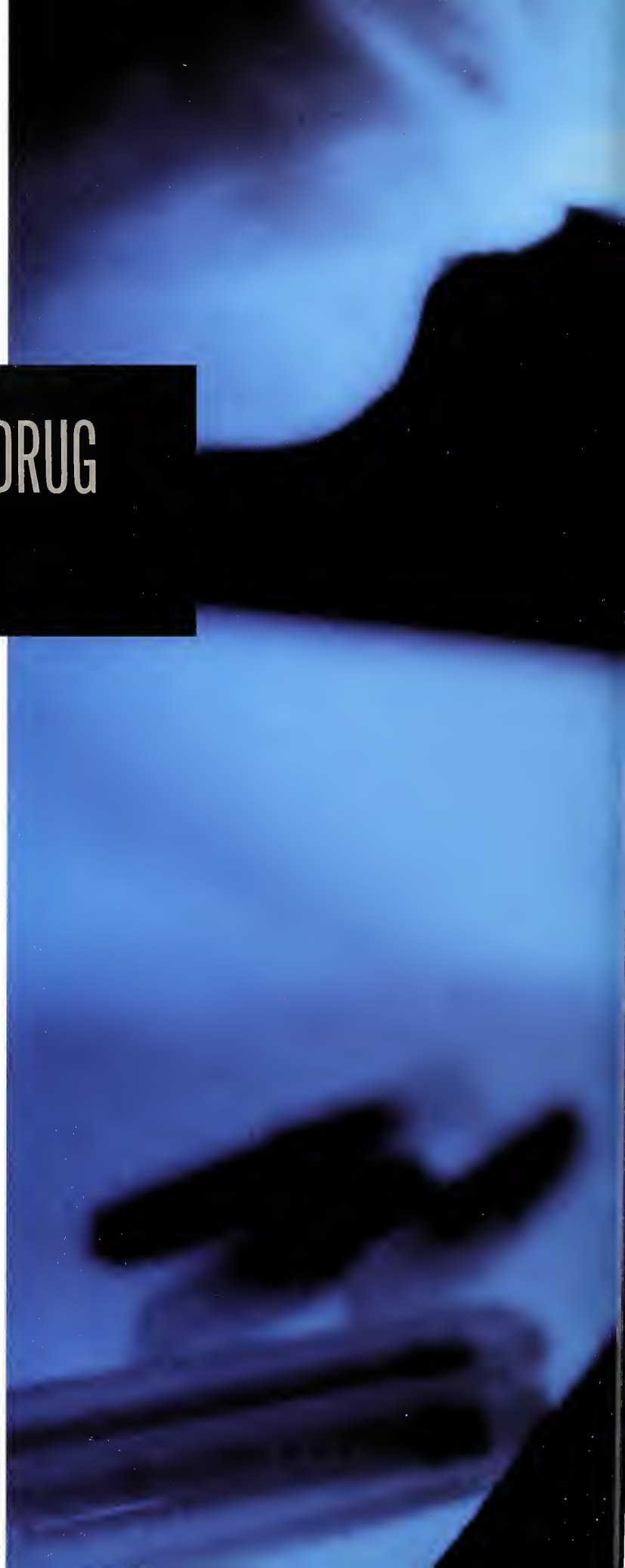
ANTIVIRAL DRUG RESEARCH

Viruses cause the most common acute infectious illnesses in the United States and are responsible for a number of persistent infections. New viruses that cause diseases ranging in severity from mild to lethal continue to be discovered. Furthermore, there is mounting evidence that viruses have a role in certain chronic diseases. Thus the need for effective drugs for the treatment and prevention of viral diseases has assumed growing importance.

Very few drugs have been found that will destroy or inhibit the growth of viruses without also destroying host cells. However, scientists have devised new approaches based on advances in the scientific understanding of the molecular biology of virus replication. It is now theoretically possible to design antiviral compounds that act directly or indirectly on the biosynthesis or replication of the viral genome. Most of the currently available agents are quite toxic and can be used clinically only under certain limited circumstances. NIAID is emphasizing research on the development and testing of new, targeted antiviral agents that will interfere with viral pathogenicity but will have minimal deleterious effects on the host cell. In addition, the efficacy of biological response modifiers such as interleukin-2 and the interferons is being evaluated.

Research on New Drugs for AIDS

NIAID has mounted a vigorous effort to identify antiviral drugs for use in the treatment of AIDS. In collaboration with the United States Army Research Development Command, NIAID established a large-scale, rapid, *in vitro* screening program to evaluate drugs with potential action against the AIDS virus. NIAID tests promising candidate drugs in animals with retroviral diseases similar to AIDS. In addition, the Institute supports a number of AIDS National Cooperative Drug Discovery Groups, collaborative ventures that enlist the talents of scientists from various disciplines in academia, industry, and government.



Ultracentrifuge tube contains purified, cloned varicella virus DNA.


200ml
150
100
50

Clinical Evaluation

NIAID has a long-standing interest in the clinical evaluation of antiviral substances. The NIAID Collaborative Antiviral Study Group (CASG) embraces a large number of university-based research projects that have tested drugs against various viral diseases, including herpes simplex encephalitis, neonatal herpes infection, and herpes zoster.

Studies by CASG researchers showed for the first time the clinical value of a systemic antiviral agent, vidarabine, against a serious viral disease, herpes simplex encephalitis (HSE). A rare complication of herpes simplex infection, untreated HSE kills more than 70 percent of patients and leaves few survivors with normal neurologic function. Subsequently, a CASG study showed that acyclovir, a drug recently licensed for treatment of genital herpes, offers significant advantages over vidarabine. It reduces mortality and increases the percentage of patients who ultimately either return to normal function or have manageable impairment. Even so, fewer than half of the patients treated with acyclovir recover completely. CASG investigators are planning to evaluate the efficacy of the two drugs used in combination.

They are also studying the use of acyclovir against neonatal herpes infections. The disease, which occurs in infants born to mothers with genital herpes, affects 1,000 babies each year in the United States. Neonatal herpes can affect the central nervous system, leading to mental retardation or death. It can be disseminated throughout the body or can be restricted to the skin, eyes, and mouth.

Other Antiviral Studies

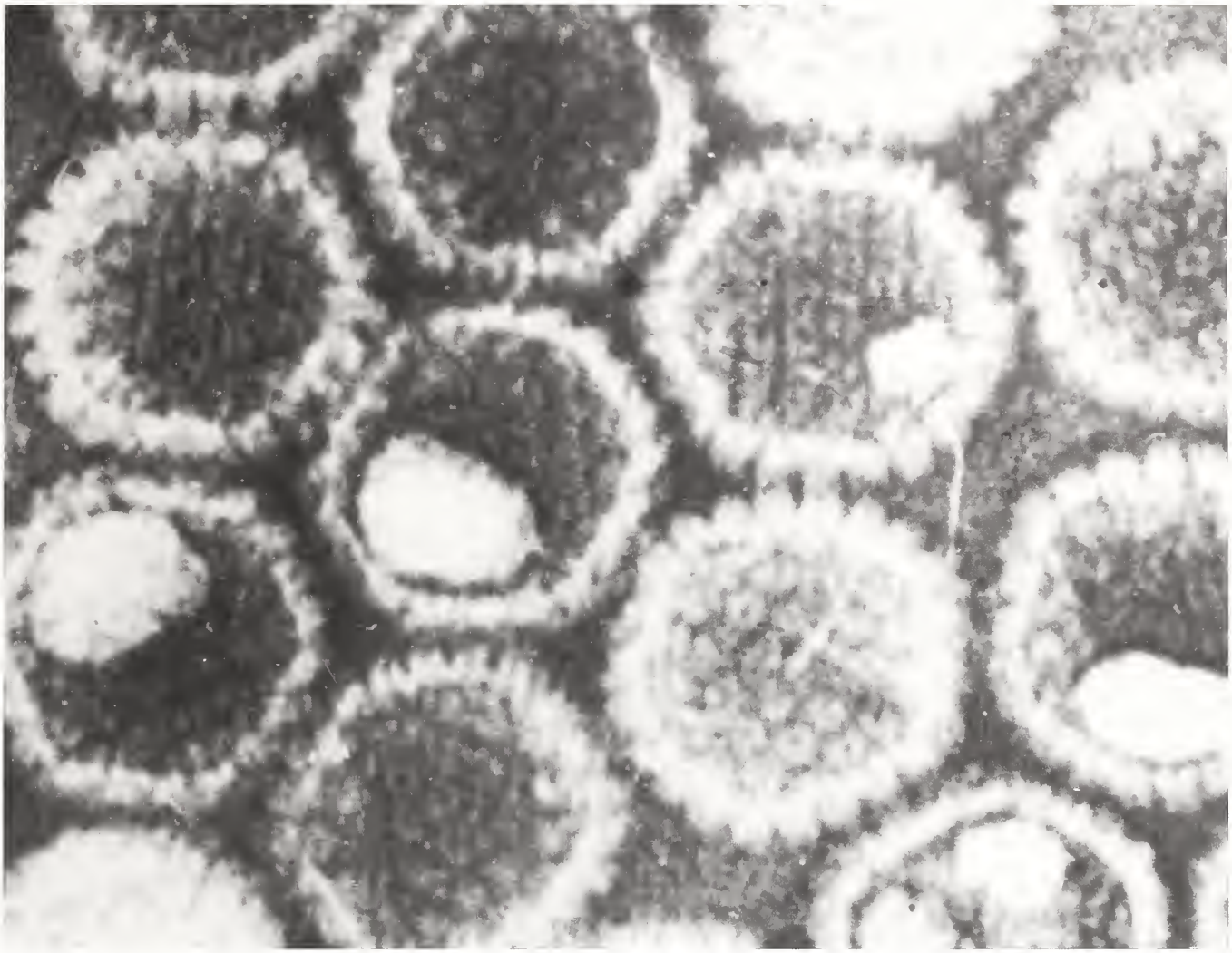
Herpes zoster, or shingles, is caused by varicella zoster virus, which also causes chickenpox. In immunocompromised patients, the disease can become disseminated and threaten life. Herpes zoster also affects healthy persons, primarily the elderly, and can be very painful. NIAID is comparing treatment with acyclovir or steroids, or a combination of the two, to promote healing and reduce pain.

NIAID-supported investigators are analyzing the mechanisms of action of amantadine and rimantadine, two drugs that are effective in preventing and treating influenza A infections, and the efficacy of lymphokines against diseases caused by papillomaviruses and herpesviruses. The Institute has also supported studies showing that interferon can help to prevent the common cold. The primary drawback is that continuous use of interferon in doses sufficient to be effective can result in unacceptable side effects.

Animal Models

Through a number of contracts, NIAID is supporting the development of animal models of various human diseases, including varicella, cytomegalovirus, herpes, AIDS, and influenza. These models will provide a ready mechanism for the screening and evaluation of new antiviral drugs prior to clinical trials. They are available to academic and industrial investigators requesting evaluation of specific compounds.

At the University of Alabama, Birmingham, Richard Whitley, M.D., discusses antiviral protocols with biostatistician Seng-jaw Soong, Ph.D. Dr. Whitley heads the NIAID Collaborative Antiviral Study Group and also heads an AIDS National Cooperative Drug Discovery Group.



Herpes simplex virus (type 2).

Viruses

Viruses are minute particles of genetic material (either DNA or RNA) surrounded by a protein coat. Only by invading and taking over living cells, which have components that viruses lack, are they able to reproduce. The ability of a virus to enter a particular cell depends on whether the cell has specific receptor sites to which that virus can attach itself. As new viral particles are made, they either emerge from the cell one by one, without major damage to the cell, or they cause the cell to burst open and die. Sometimes viruses remain dormant or latent within a cell, without producing virus particles.

A human or animal attacked by a virus can react in different ways, depending on the amount of infecting virus and its site of entry, the number and kinds of cells infected, the nature of the cell-virus interaction, and the state of the host's immune response. The effect of a given virus in different individuals may range from inapparent infection to death.

Stephen Straus, M.D., intramural scientist, counsels participants in a study of acyclovir in management of genital herpes episodes.

INTERNATIONAL HEALTH AND TROPICAL DISEASES

NIAID has a long tradition of involvement in international health, both from the standpoint of humanitarian concern and scientific interest. Research on infectious and parasitic diseases and disorders of the immune system that are especially prevalent in developing countries provides information that is applicable to medical problems of the industrialized world as well.

Diarrhea in children, acute respiratory infections, and the many diseases that can be prevented by immunization cause widespread suffering and death in developing countries. NIAID is committed to vigorous efforts to develop new and more affordable vaccines and improved treatment approaches to combat these problems.

Tropical diseases, especially those caused by parasites, afflict nearly 1 billion people in the world. Research conducted and supported by NIAID on parasitic and fungal diseases has become especially relevant with the advent of AIDS. Due to their underlying immunodeficiency, persons with AIDS fall prey to a wide spectrum of parasitic, fungal, viral, and bacterial infections, known as opportunistic infections. Researchers are also studying how such infections may act as cofactors in the progression of latent or low-level infection to full-blown AIDS.

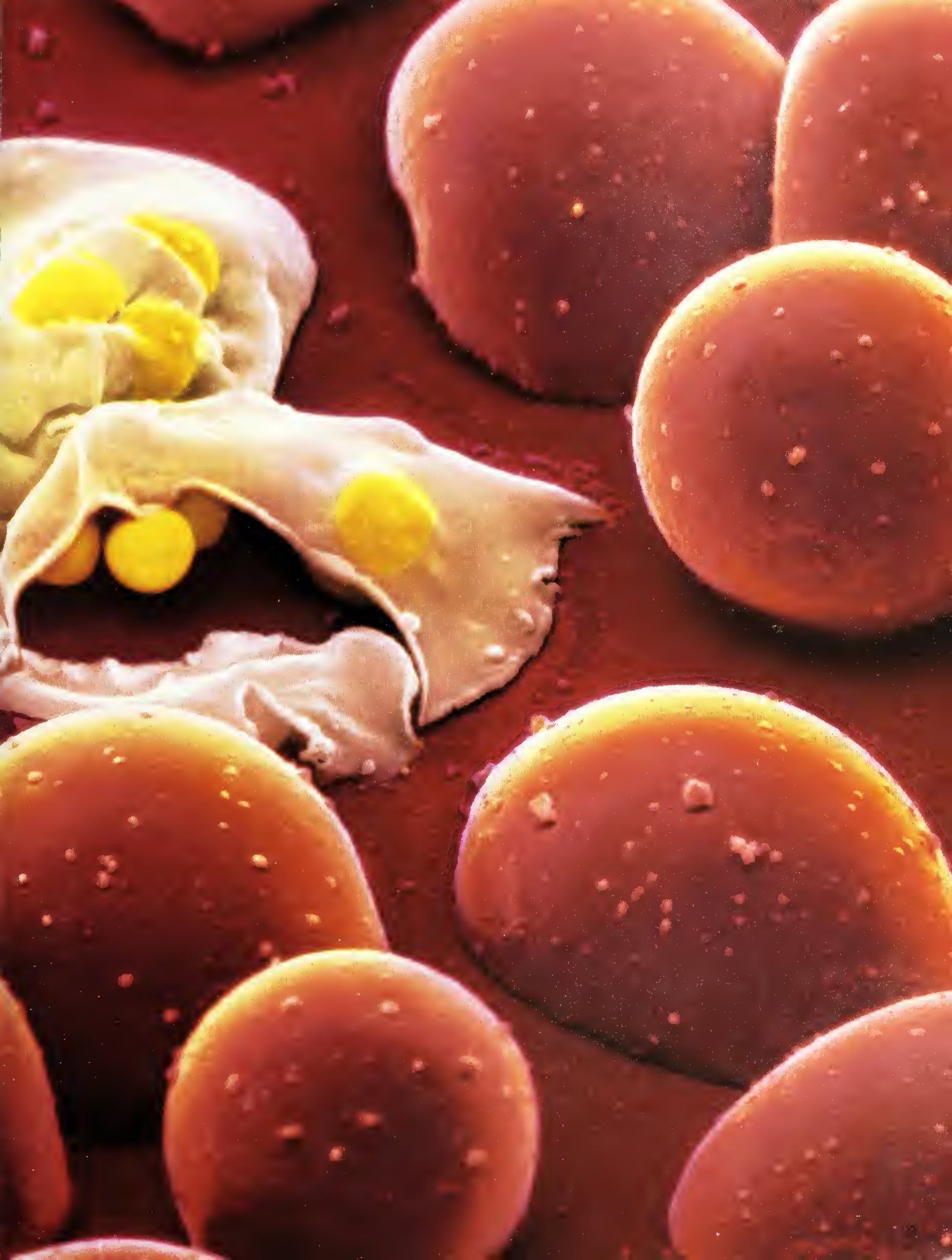
Close working relationships between many specialists in the United States and abroad are of paramount importance in solving the health problems of the Third World. NIAID offers many opportunities for fruitful collaboration among physicians, parasitologists, immunologists, entomologists, sanitarians, and epidemiologists in studying the complex interactions of disease agents, the environment, insect vectors, and human behavior.

Malaria Research

Thirty years ago, there was great optimism that malaria could be eradicated through the use of powerful insecticides and synthetic antimalarial drugs. Now, chiefly because the mosquitoes that carry malaria parasites have become resistant to many insecticides and the most deadly malaria parasite has become drug resistant, the disease has regained its hold in many countries. Hundreds of millions of people suffer from debilitating malaria infection, and 1.5 to 2 million die each year.

Nearly a third of the world's population lives in malaria-endemic areas, primarily in Africa, Asia, and Central and South America. Americans visiting or working in these areas increasingly risk contracting malaria.

Malaria-infected red blood cells burst open, releasing infectious parasites.

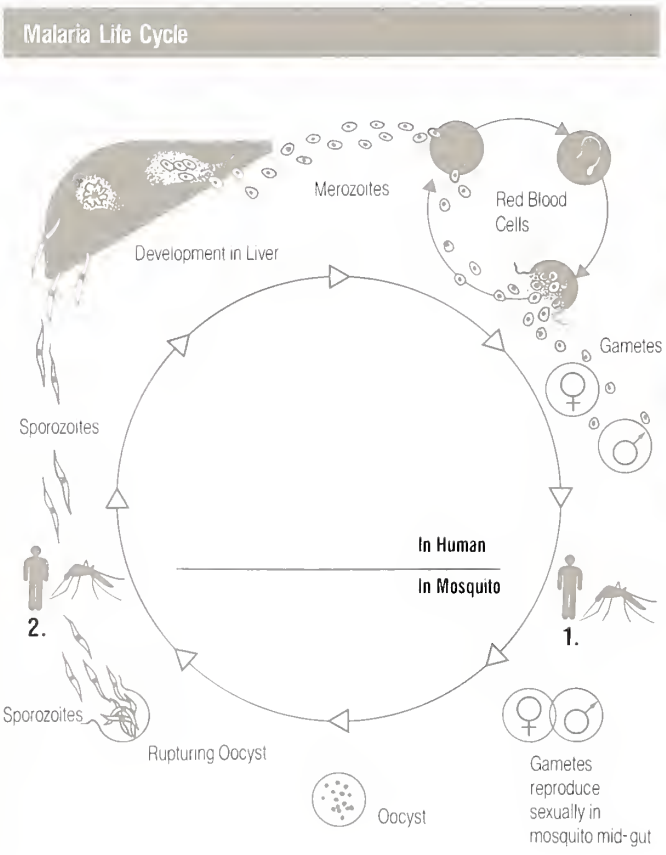


Both the magnitude of the problem and the setbacks in control and prevention have spurred efforts to develop vaccines against malaria. Research is complicated by the fact that there are several stages in the life cycle of each of the four parasite species that cause human malaria (see illustration). These different stages offer research opportunities, however, as each stage appears to have several antigens against which vaccines could be targeted. It is possible that an effective antimalarial vaccine may have to contain several components.

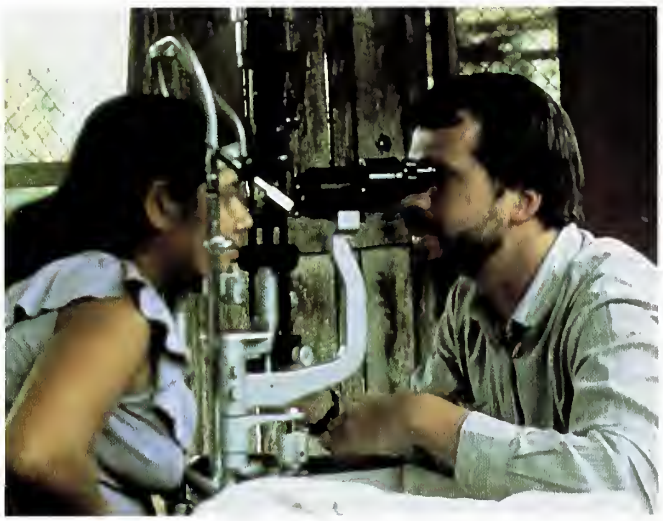
Because culture of the parasite for antigen production is either impossible or limited to small amounts, malaria vaccines must be produced through recombinant DNA technology or synthesis of antigenic peptides. NIAID intramural scientists and grantees have identified antigens found on the surface of the sporozoite of *Plasmodium falciparum*, the most dangerous species of malaria. Through gene cloning or chemical synthesis, they have produced polypeptides that stimulate immune response. Vaccines using these polypeptides are being tested in human volunteers.

Increased understanding of the immune response to the antigens of each life cycle stage has led to other vaccine approaches. NIAID scientists are developing a means of blocking transmission of the parasite by eliciting antibodies to gametes and zygotes (fertilized gametes) in the infected mammalian host. These antibodies do not protect the host, but when ingested by mosquitoes along with the blood meal, the antibodies react against parasites developing in the mosquito gut. Scientists are also investigating methods of combining malaria vaccines with adjuvants, substances that boost immunogenicity.

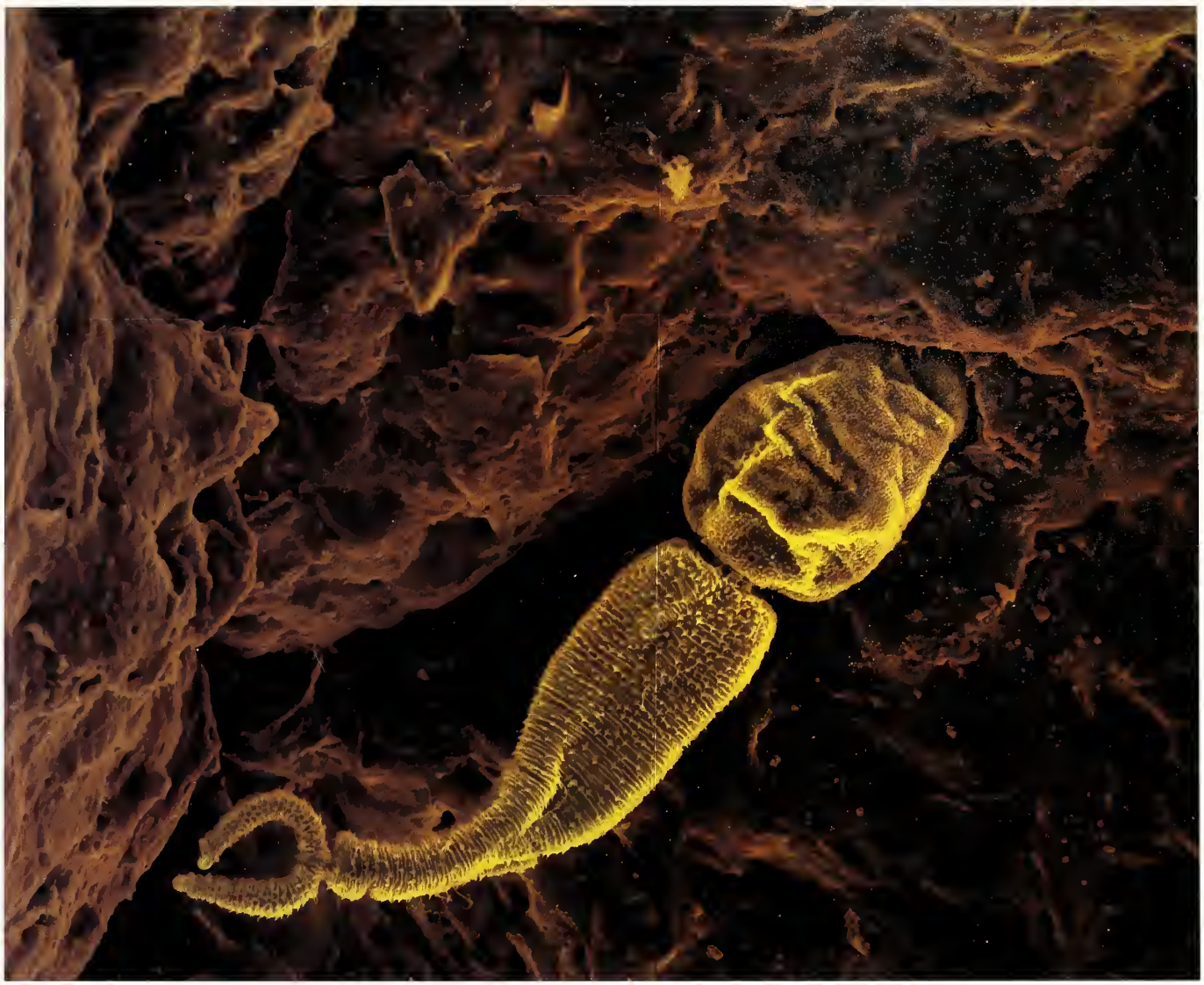
A different way to control malaria might be through breeding anopheline mosquitoes that are incapable of transmitting infection. NIAID scientists identified a mosquito strain that has a genetically controlled ability to "recognize" living malaria parasites and render them harmless by encapsulating them. Having developed a technique for inserting genes into mosquito chromosomes, the investigators will attempt to introduce genes from the refractory mosquito strain into mosquito varieties that are principally responsible for transmitting the malaria parasite.



When mosquito bites malaria-infected human (1), it ingests gametes, which reproduce in mosquito mid-gut and produce oocysts. Oocysts rupture, releasing sporozoites, which move to mosquito salivary gland. When mosquito takes another blood meal (2), sporozoites are injected into human and migrate to human liver. Merozoites, produced in liver, infect red blood cells. Following red blood cell cycle, gametes are released into blood and cycle repeats.



In Guatemala, NIAID is searching for evidence of protective immunity against onchocerciasis, a filarial disease that is a major cause of blindness in Central and South America and Central and West Africa.



A schistosome larva migrates through the blood vessels to the lungs, then to the liver, where it matures into an adult worm, and finally to the blood vessels of the intestine or bladder. The hundreds of eggs produced daily by each male-female pair of worms provoke inflammation and formation of fibrous tissue.

New Prospects for Schistosomiasis Vaccine

NIAID scientists have made significant contributions to the development of a vaccine for schistosomiasis, also caused by a parasite with a complex life cycle. Humans are infected through contact with fresh water containing the larval form of the parasite. The ensuing disease can eventually damage the urinary and gastrointestinal tracts, the liver and sometimes the central nervous system. Even after treatment, reinfection occurs rapidly in endemic areas, particularly among children.

Animal testing of candidate vaccines for schistosomiasis is less difficult than for malaria, as schistosomes that infect humans can be grown readily in experimental animals. NIAID scientists cloned a gene for a schistosomal antigen that when purified and injected into mice induces partial protective immunity against infection. The antigen was identified as paramyosin, a muscle protein present in schistosomes and other invertebrates.

NIAID scientists have documented resistance of the parasite to one of the more commonly used drugs for schistosomiasis, and are employing DNA probes to investigate the genetic basis of drug resistance and susceptibility.

Leishmaniasis

Leishmaniasis is a skin disease caused by protozoa transmitted by the bite of the sandfly. It most often occurs in Central and South America and the Middle East, where sandflies can be found in habitats ranging from jungles to desert areas.

The disease assumes two main forms: cutaneous and visceral. The first, characterized by skin lesions that vary in severity and extent, is generally self-limiting but can be chronic. This type can also emerge years after the initial infection in the form of mucocutaneous lesions, causing severe, sometimes fatal, damage to the upper respiratory tract. The second form of leishmaniasis, also known as kala-azar, is a chronic, debilitating disease that affects the spleen, liver, bone marrow, and lymph nodes. Kala-azar is nearly always fatal if not treated.

Scientists in NIAID's laboratories are defining the protective and immunopathologic immune responses to leishmaniasis in a mouse model. They have developed an effective vaccine, and in subsequent studies have found that only a small subset of the T cells stimulated by leishmanial antigens induce protective immunity. Other studies in mice suggest that a regulatory T cell imbalance and defects in production of macrophages are responsible for the failure of lesions to heal.

Chagas' Disease

Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi* and transmitted by blood-sucking reduviid bugs, is a major health problem in several Latin American countries. While the majority of infected persons recover without long-term complications, a significant number develop severe cardiac or esophageal disease a number of years later. The pathogenesis of these chronic manifestations is a critical research question.

Research conducted at NIAID by Franklin Neva, M.D., may explain why some patients with leishmaniasis have nonhealing lesions.

Allen Cheever, M.D., conducts schistosomiasis studies in mice.

U.S. - Japan Cooperative Medical Science Program

In 1965 the governments of the United States and Japan established an international program to improve the health of the people of Asia through joint research efforts. Panels including biomedical scientists from both countries review progress and set research objectives for cholera, leprosy, malnutrition, AIDS, parasitic diseases, tuberculosis, hepatitis, viral diseases (rabies, dengue, and gastroenteritis), immunology, and environmental mutagenesis and carcinogenesis. Each country supports its own scientific projects. NIAID assumed full responsibility for the administrative management and funding of the U. S. part of the program in 1968.

A number of researchers have studied the acute phase of Chagas' disease in experimental animals. Recently, NIAID scientists have demonstrated that some of the clones of single parasites can cause severe heart disease that is similar to the chronic disease in humans. Possibly, they speculate, only certain strains of the parasite cause the chronic heart and gastrointestinal diseases.

Collaborative Programs with Other Countries

For some time, NIAID has conducted numerous studies in areas of the world where parasitic and other tropical diseases are common. Many of these projects involve collaboration with universities and scientists in other countries, and receive additional support from national and international agencies and foundations. A long-term collaborative program in Sudan focusing on malaria, schistosomiasis, leishmaniasis, and onchocerciasis has provided unique opportunities for training in clinical and contemporary research approaches to tropical disorders for American and Sudanese staff and has generated many scientific publications.

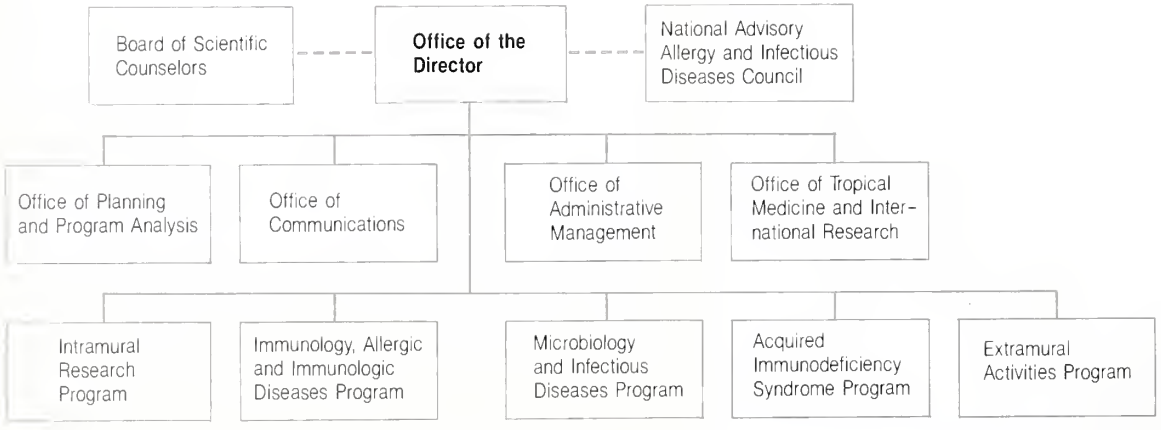
Egyptian, Israeli, and NIAID scientists are cooperating in a project on the epidemiology and control of vector-borne diseases such as leishmaniasis, malaria, and Rift Valley fever. And in Peru, NIAID is sponsoring a collaborative study of typhoid fever, shigellosis, and other diarrheal diseases.

A long-term study to improve understanding of the immune system's role in leprosy is being conducted by NIAID and Indian scientists. Leprosy, which can be treated effectively if diagnosed early, can have a latent period of years between infection and appearance of symptoms. Scientists have learned that the manifestations and communicability of the disease are closely correlated with the patient's ability to mount a normal immune response to the leprosy bacillus.

Trials of new drugs and combinations of drugs for bancroftian filariasis, a parasitic disease transmitted by mosquitoes, are also being conducted in India. In addition, NIAID scientists are attempting to identify an antibody that appears to block infection in some filariasis patients.

Through an international collaborative program, NIAID awards grants to American institutions, which in turn sponsor AIDS research in countries where the disease is epidemic or endemic. The program enables U.S. experts in virology, epidemiology, medicine, and public health to spend up to two years in other countries, helping to train scientists and aiding in the development of AIDS research projects and facilities.

Organization of National Institute of Allergy and Infectious Deseases



Intramural and Extramural Programs of NIAID

NIAID is one of the 12 Institutes of the National Institutes of Health, the primary medical research arm of the U. S. Public Health Service.

NIAID conducts and supports a significant proportion of the federally funded research contributing to a better understanding of the causes of allergic, immunologic, and infectious diseases and to the development of better means of preventing, diagnosing, and treating these illnesses. Approximately 80 percent of its budget is allocated to extramural research and training grants and contracts to scientists in medical schools, universities, industry, and private research institutions, primarily within the United States. While the majority of grants are awarded for investigator-initiated studies, the Institute also solicits grant applications and contract proposals for targeted research projects.

To fulfill its mission, the Institute's extramural activities are organized into three major scientific programs: the Immunology, Allergic and Immunologic Diseases Program; the Microbiology and Infectious Diseases Program; and the Acquired Immunodeficiency Syndrome Program. These programs support studies in most of the basic fields of medical research, including biology, immunology, immunopathology, immunogenetics, virology, microbiology, molecular biology and biochemistry.

In addition, NIAID intramural scientists and physicians conduct research in 15 laboratories at the NIH campus in Bethesda, Maryland, and at the Rocky Mountain Laboratories in Hamilton, Montana. Researchers have access to highly sophisticated laboratory equipment and, at the Bethesda campus, to research hospital facilities at the NIH Clinical Center, the library facilities of the National Library of Medicine and the NIH, and individual reference libraries located in each laboratory. The facilities of the NIH Division of Computer Research and Technology are accessed by a network of terminals, and several laboratories operate computers of their own.

Much of the research conducted and supported by NIAID is planned and performed at the level of basic science. Research that has developed to the point of clinical application is pursued in studies with patients, including clinically controlled trials. These studies are often performed in collaboration with research institutions in the United States and abroad, as well as in the NIH Clinical Center.

The directors of each program are responsible for the planning and overall management of their particular areas. Because of the natural overlapping of scientific disciplines, the program directors work closely to coordinate ongoing programs and develop new research areas.

Arye Rubinstein, M.D., of New York's Albert Einstein College of Medicine, site of one of NIAID's AIDS Clinical Trials Units, is a specialist in the treatment of children with AIDS.

National Advisory Council

The National Advisory Allergy and Infectious Diseases Council plays a very important role in shaping the research directions of the Institute. Members of the Council are leading medical or scientific experts in the fields of allergy, immunology, and infectious diseases, and representatives of the lay community who have demonstrated an interest in the research areas of NIAID. It provides final review of applications for research and research training grants and recommends the approval of applications that merit support. In addition, the Council makes recommendations to the Director, NIH, concerning programs, policy, and activities in the areas of AIDS, immunology, allergic and immunologic diseases, microbiology, and infectious diseases. Advisory Council members are selected by the Director, NIH, and serve for overlapping 4 year terms.

The Advisory Council is divided into standing subcommittees that meet three times a year at the time of the Council meetings to review grant applications and to make recommendations to the full Council.

Research Review Committees

Initial scientific and technical review of contract proposals and grant applications for special research programs, including program projects, centers, institutional National Research Service Awards, conference proposals, and special development award programs, is provided by the Allergy, Immunology, and Transplantation Committee, the Microbiology and Infectious Diseases Research Committee, and the Acquired Immunodeficiency Syndrome Committee. Committee members, who are experts in relevant scientific disciplines, are appointed by the Director, NIH, for overlapping 4 year terms.

Board of Scientific Counselors

Nongovernmental expert review of NIAID's intramural research program is provided by the Board of Scientific Counselors, composed of authorities knowledgeable in the fields of microbiology, immunology, and clinical research in allergic and infectious diseases. The Board members, who are appointed by the Director, NIH, for overlapping 4 year terms, make periodic visits to NIAID laboratories to assess research in progress and evaluate the productivity and performance of staff scientists.

Grant Application Review Process

The application review process at NIH, called the peer review system, ensures the support of the highest quality biomedical research. It is a dual system consisting of initial review of scientific merit followed by secondary review with regard to program relevance, significance of the research, and priority in relation to the Institute's mission. Thus scientific review is separated from policy recommendations. This is a highly competitive process that relies on the dedication of basic and clinical research scientists who are acknowledged authorities in their fields and who are willing to serve as peer reviewers. Steps in the peer review process are:

—Applications for funding are received by the Division of Research Grants (DRG), NIH, which refers all applications to appropriate Institutes for funding consideration and assigns applications to an initial review group (IRG), also known as a study section, for assessment of scientific work. Each of the more than 60 IRGs consists of nongovernment scientific experts.

—After the review process is completed, each approved application is assigned a priority score. A narrative summary of reviewer comments is prepared and transmitted to the Institute to which the application has been assigned.

—The summary statement, with any additional comments or materials, is submitted to the Advisory Council. The applicant also receives the summary statement.

—The Advisory Council performs a secondary policy and program review and makes a recommendation on the application.

—The Institute Director acts on the recommendation of the Advisory Council.

Detailed information and eligibility criteria on awards of grants and contracts may be obtained from the Division of Research Grants, National Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892. Application kits containing detailed instructions and application forms are available at the grants and contracts offices of research institutions or from the NIH Division of Research Grants.

NIAID Research Project Grants Awards
FY 1978 - 1987
(Dollars in Thousands)

Fiscal Year	Amount
1978	$ 85,675
1979	112,054
1980	132,677
1981	150,322
1982	152,988
1983	180,630
1984	206,852
1985	245,266
1986	244,453
1987	340,854

NIAID Budget Actual Obligations
FY 1978 - 1987
(Dollars in Thousands)

Fiscal Year	Amount
1978	$161,814
1979	191,119
1980	214,657
1981	232,028
1982	235,835
1983	278,939
1984	319,593
1985	370,047
1986	367,142*
1987	545,433

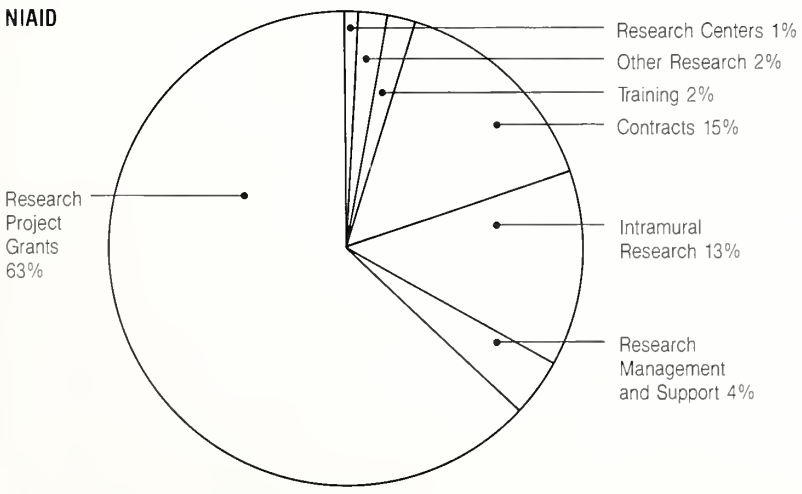
*excludes $37,373,000 reimbursement for AIDS from Office of the Director, NIH

NIAID Competing Research Project Grants
FY 1978 - 1987

Fiscal Year	Number of Grants Reviewed	Number of Grants Council Recommended for Approval	Number of Grants Awarded
1978	1,255	1,091	397
1979	1,238	1,104	537
1980	1,313	1,181	452
1981	1,374	1,242	433
1982	1,550	1,437	411
1983	1,519	1,406	522
1984	1,498	1,408	507
1985	1,635	1,504	549
1986	1,713	1,580	540
1987	1,834	1,738	641

Fiscal Year 1987 Actual Obligations

NIAID



NIH Publication No. 88-2773
June 1988