The Connection

There is no doubt that oral health and general well-being are inextricably bound. Many conditions that plague the body are manifested in the mouth, a readily accessible vantage point from which to view the onset, progress, and management of numerous systemic diseases.
What does this mean for traditional dental research? It means that perhaps this term is an anachronism, that it limits the field of inquiry to only the teeth and surrounding tissues, that the word "traditional" no longer applies. In fact, there is nothing traditional about the science of the oral, dental and craniofacial tissues. The teeth and gingiva (gums) are but one vital part of a remarkably dynamic system that touches on virtually every biomedical and behavioral discipline. Research in virology, immunology, genetics, biochemistry, developmental biology, and many other fields is carried out by men and women whose names end in PhD, DDS, and MD. They are laboratory researchers. They are patient-oriented clinical scientists. They see the beauty and order of a world at its molecular level. They engineer genes to correct nature's mistakes. Their educational backgrounds and training experiences are as diverse as the diseases and systems they study. What these scientists share in common, however, is the recognition that oral health is not an independent entity cut off from the rest of the body. Rather, it is woven deeply into the fabric of overall health.

The Body's Silent Alarm

One human mouth is home to more microorganisms than there are people on our planet earth. The wide array of habitat renders the mouth a microbial paradise, offering preferred accommodations on the cheek, or on the back of the tongue in an anaerobic crevice, or in the moist, oxygen-deprived area between the tooth surface and the adjacent periodontal tissues.
The mouth's microbial ecology, however, is extremely sensitive to the challenges that confront its human host throughout the lifespan and, therefore, can often change precipitously. From fetal life through senescence, the mouth's continued exposure to opportunistic infectious pathogens is in balance with host immunity; the balance between these profoundly important processes often serves as a mirror for the detection of not only oral pathology, but also major systemic diseases.
It is especially in the soft tissues that this relationship is played out. The lips, tongue, gums, salivary glands, and oral mucosa can all warn of trouble in our general health. Because of their exquisite positioning in the body, these tissues and their fluids form a protective barrier of mucosal immunity to the outside world that when breached, signal clinical disease. They tell of direct assaults by a broad range of systemic disorders such as diabetes, AIDS and Sjögren's syndrome, as well as complications of treatments like cancer chemotherapy and radiation. For some disorders, particularly AIDS and diabetes, oral tissues may reveal lesions or pathology that are the first signs of systemic disease.

Oral Opportunistic Infections: Links to Systemic Diseases

The periodontium, comprised of the gingiva, bone and other supporting tissues that anchor the teeth, plays a key role in the interplay between oral health and systemic disease. Infection in these tissues, primarily by gram-negative anaerobic bacteria, can initiate a series of inflammatory and immunologic changes leading to the destruction of connective tissue and bone. Long considered a localized infection, periodontal diseases are now linked to a variety of conditions with systemic implications.

Chronic Degenerative Diseases

Periodontitis, advanced infection of the periodontium that often causes tooth mobility and tooth loss, appears to share genetically determined risk factors with several other chronic degenerative diseases such as ulcerative colitis, juvenile arthritis, and systemic lupus erythematosus. Recent research points to specific genetic markers associated with increased production of the pro-inflammatory cytokines interleukin-1 and TNF as strong indicators of susceptibility to severe periodontitis. This recent finding could lead to early identification of people at most risk for severe periodontal disease and initiation of appropriate thera peutic interventions.

Diabetes Mellitus

The destructive inflammatory processes that define periodontal disease are closely intertwined with diabetes.

Persons with noninsulin-dependent diabetes mellitus (NIDDM) are three times more likely to develop periodontal disease than nondiabetic individuals. Add smoking to the mix, and the chances of developing periodontitis with loss of tooth-supporting bone are 20 times higher. An increased risk for destructive periodontal disease also holds for persons with insulin-dependent diabetes mellitus (IDDM).

Much of what is known about the periodontal complications of diabetes has been learned from the Pima Indians of Arizona, who have the highest reported rates of NIDDM in the world. NIDCR-supported research in the Pima community has shown that periodontal infection is more prevalent, more severe, and develops at an earlier age in this population than in nondiabetic persons. As diabetes increases in severity, the rate at which vital tooth-anchoring bone is lost accelerates. Pima Indians with NIDDM are 15 times more likely to be edentulous than those without diabetes.

Now there is evidence that a history of chronic periodontal disease can disrupt diabetic control, suggesting that periodontal infections may have systemic repercussions. The exact nature of this complex relationship is not clear. It is likely, however, that increased genetic susceptibility to infection, impaired host response, and the excessive production of collagenase found in periodontal disease may all play important roles in NIDDM. Similarities in the etiology of periodontal and other complications of diabetes have also emerged.

Studies have shown, for example, that hyperglycemia is the common basis for diabetic complications in the eyes, kidneys and nerves. Glucose in high concentrations attaches to other molecules, stimulating chemical reactions that produce advanced glycosylation end products. These large molecules accumulate in tissues, causing damage and disrupting normal function. Scientists suspect that these cellular reactions figure as well in the tissue destruction seen in periodontal disease.

Investigators are also examining the interplay between periodontal infection and metabolic control. Acute viral and bacterial infections are known to induce insulin resistance, which disrupts blood glucose control. Factors including stress, fever, catabolism, and elevated levels of hormones antagonistic to insulin such as growth hormone, cortisol, and glucagon likely play a role in the development of insulin resistance during infection.

It is possible, then, that chronic gram-negative infections with persistent production of bacterial toxins, like periodontal disease, could have the same deleterious effect. If so, would elimination or control of periodontal infection improve metabolic control of diabetes?

To explore this hypothesis, researchers designed a treatment protocol specifically to manage diabetes-associated periodontitis in a group of Pima Indians with poorly controlled NIDDM. They found that debridement (deep cleaning to remove hardened plaque below the surface of the gingiva), combined with an antimicrobial solution and a 2-week regimen of the antibiotic doxycycline -- chosen for its anticollagenase activity -- resulted in significant short-term improvement in the concentration of hemoglobin A1c, a measure of average blood glucose levels over 3 months.

A control group receiving only debridement did not share the gains in periodontal health, improved hemoglobin A1c levels, and reduced hyperglycemia that the treatment group experienced.

These findings offer evidence that chronic infections such as periodontal disease worsen glycemic control and that eliminating these infections could enhance metabolic control in persons with diabetes. Additional large-scale studies are needed to further evaluate the effects of treating periodontitis on blood glucose levels. Future research should also examine, in other populations, the relationship between severe periodontal disease and poor glycemic control that has been evidenced in the Pima Indian community.

While work proceeds on the oral complications of diabetes, other studies are exploring the molecular pathogenesis of the disease. NIDCR researchers have identified an important marker protein, IA-2ß, for insulin-dependent diabetes mellitus, an autoimmune disorder which affects close to one million people in the United States alone.

Destructive autoantibodies, which attack the body's own insulin-producing beta cells, are the basis of the existing, labor intensive diagnostic test for IDDM. However, the recent identification of target proteins in the pancreas, such as IA-2ß, that react with these autoantibodies makes it possible to develop a rapid and effective test to screen large populations for IDDM.

IA2ß, when used in combination with two other known marker proteins, IA-2 and GAD 65 , recognized autoantibodies in 90 percent of persons with IDDM. The presence of autoantibodies to the marker proteins in otherwise normal individuals was also highly predictive in identifying those at risk of developing the disease. In addition, these proteins are candidates for immune tolerance studies, which attempt to prevent the development of destructive autoantibodies and subsequent IDDM.

The investigators are hopeful that their demonstration of the proteins as major targets of the autoimmune attack will aid in uncovering the actual cause of the disease process.

Heart Disease

A number of studies have shown that people with periodontitis are more likely to develop cardiovascular disease than individuals without periodontal infection. One such study suggests that the risk of fatal heart disease doubles for persons with severe periodontal disease.
Part of the link between these two diseases may be discovered through novel investigations of the opportunistic, infectious bacteria that colonize the mouth. Scientists theorize that certain types of these bacteria, which form biofilms and cause periodontal disease, also activate white blood cells in the body to release pro-inflammatory mediators that may contribute to heart disease and stroke.
To explore the underlying inflammatory responses common to both diseases, NIDCR grantees are examining periodontal disease measures (pocket depth where gingival tissues have pulled away from tooth surfaces and where there is loss of tissue) and biological responses in 14,000 people enrolled in an extensive study of heart disease sponsored by the National Heart, Lung and Blood Institute. Scientists will also analyze gingival crevicular fluid constituents that may contain pro-inflammatory mediators associated with heart disease, as well as blood samples to identify antibodies to periodontal pathogens.
The research team will compare these measures with clinical indicators of heart disease, ultrasound measures of carotid vessel thickening, and the occurrence of heart attacks, stroke, and death to determine if there is a correlation. Should the link between oral disease and heart disease be firmly established, future studies will focus on identifying the specific biological factors involved and transferring this knowledge to prevent disease.

Preterm Low Birth Weight Babies

Emerging evidence may link severe periodontal disease in pregnant women to a sevenfold increase in the risk of delivering preterm low birth weight babies. NIDCR-supported researchers estimate that as many as 18 percent of the 250,000 premature low-weight infants born in the United States each year may be attributed to infectious oral disease.
The emotional, social, and economic costs associated with these small babies are staggering. Hospital costs alone surpass $5 billion annually. When costs to society in terms of suffering and managing long-term disabilities often associated with prematurity are considered, this figure escalates dramatically.
In a recent study, mothers of preterm low-weight newborns were found to have significantly more severe periodontal disease than did mothers of full-term, normal weight babies. Investigators believe that the molecular pathogenesis may be similar to that characterized for other maternal, bacterial, opportunistic infections, such as genitourinary infections, that are associated with low-weight preterm births.
Scientists theorize that oral pathogens release toxins that reach the human placenta via the mother's blood circulation and interfere with fetal growth and development, which has been shown to occur in animal studies. The oral infection also prompts accelerated production of inflammatory mediators PGE 2 and TNF that normally build to a threshold level throughout pregnancy, then cue the onset of labor. Instead, the elevated levels of these inflammatory mediators trigger premature delivery.
Taking into account all the known risk factors for premature birth, the researchers could identify no other reason for the relationship they had found between severe periodontal disease and preterm low-weight births. Additional research is needed to confirm this intriguing finding and to determine if treating and preventing periodontal disease would reduce the incidence of these high risk births.

Acquired Immunodeficiency Syndrome

The oral effects of systemic disease are by no means limited only to the periodontium. All of the tissues in the oral cavity are fair game for a variety of insults, either directly from infection, or indirectly as part of the systemic disease process. There is perhaps no better illustration of the involvement of oral tissues in systemic disease than the oral manifestations of AIDS.

Oral Lesions

Since the acquired immune deficiency syndrome was first recognized in the United States in 1981, the mouth has provided a remarkable laboratory for the study of this emerging infectious disease that targets the immune system for destruction. The first clinical reports of this syndrome indicated that lesions in the oral cavity were common and often occurred early in the course of the disease. Oral health scientists initiated not only clinical studies to define the oral signs and symptoms, but also a basic research strategy to understand the molecular virology and immunology of AIDS.

Studies of the natural history and epidemiology of HIV/AIDS documented that the fungal disease oral candidiasis is the most common opportunistic infection seen in HIV-infected patients, followed by a second oral lesion termed hairy leukoplakia. A whitish lesion frequently seen on the side of the tongue, hairy leukoplakia is strongly associated with the Epstein-Barr virus and is a reliable predictor of AIDS.

A comparison of HIV-positive patients with similar CD4 counts (a measure of the body's immune response) revealed that those with oral candidiasis or hairy leukoplakia tend to develop major opportunistic infections or progress to AIDS more rapidly than patients without these lesions. Also, the odds of developing oral candidiasis increase as the CD4 counts of infection-fighting T cells decrease. In parts of the world where diagnostic blood tests for HIV are not available, the presence of these oral lesions in otherwise asymptomatic adults can be used as an indicator of HIV infection.

A number of studies are examining candidal species to determine the mechanisms involved in the conversion of this harmless fungus commonly found in the mouth to an aggressive infectious pathogen. NIDCR-supported research to characterize the entire genome of *Candida albicans* will accelerate this process. Other studies are focusing on drug resistant candida and the potential use of gene therapy to bolster levels of histatin, a potent anti-fungal agent normally found in the saliva. Clinical trials are also under way to determine if scrupulous oral hygiene, the use of antimicrobial mouthrinses, and regular dental care can prevent or reduce oral complications in HIV patients with severely compromised immune systems.

Anti-HIV Action

Despite the presence of HIV-associated lesions in the mouth and their implications for escalating disease, studies by NIDCR and other NIH-supported scientists suggest that HIV is not spread through casual contact with saliva. Research has shown that HIV is easily cultured from the blood and spinal fluid of AIDS patients, but not from the saliva of HIV/AIDS patients with oral lesions. Of particular interest is the finding that human saliva demonstrates anti-HIV activity.

The intense search for protective constituents in saliva led NIDCR investigators to a relatively small protein called secretory leukocyte protease inhibitor, or SLPI, which attaches to the surface of monocytes and T cells and blocks infection by HIV. SLPI may help explain why AIDS does not appear to be spread by saliva, but much about its possible protective effect remains unknown. The next steps are to determine the protein binding sites on monocytes and T cells, the role SLPI plays in HIV entry into host cells, and its potential as a protective agent against HIV transmission.

Future NIDCR directions in HIV/AIDS research include expanding both our knowledge of the natural history and epidemiology of oral transmission and manifestations of HIV in various populations (including women, children, adolescents and minorities), and our understanding of opportunistic infections and mucosal immunity. The search for therapeutic interventions, synthetic drugs and vaccines, and innovative delivery systems will also be an important part of the NIDCR research portfolio.

Binding Site Identified

Essential to progress in this area is a better understanding of just what happens at the HIV/monocyte and HIV/lymphocyte interface. One of the long-standing challenges in AIDS research has been figuring out exactly how gp120, the large protein on the surface of HIV, latches onto the CD4 target receptor on T cells in the first step in HIV infection. Studies spearheaded by NIDCR scientists have now identified that binding site, called C4, and determined how it recognizes its target receptor. These findings open the door not only for the design of new drugs and vaccines to fight HIV infection, but also for the development of interventions to block the initial interaction between HIV and cells and thereby inhibit infection.

Macrophages: HIV Reservoirs

Studies continue on the cellular and molecular mechanisms underlying immune dysfunction in HIV/AIDS, as well as on the pathogenesis of AIDS-related opportunistic infections. A new finding in this area underscores the importance of controlling opportunistic infections in AIDS patients.
It has been known for some time that CD4 T cells are the primary target of HIV infection and that their destruction leads to a weakened immune system and susceptibility to opportunistic microorganisms. As HIV infection progresses toward AIDS, the CD4 T cells are the chief source of new virus, creating a cycle of escalating virus production and T cell death. The paradox has been how the levels of HIV continue to increase over the course of AIDS, at the same time the T cell population dramatically decreases.
Investigators have now identified tissue macrophages as an unexpected source of new virus and point to opportunistic infections as a trigger that sets off a wave of HIV production. Examination of lymph nodes from AIDS patients with a variety of common opportunistic infections revealed from 5 to over 100 times the number of virus-producing macrophages than were found in the nodes of HIV patients free of such infections. The individual macrophages also demonstrated a much higher level of virus production.
Although the actual mechanism that switches macrophages from HIV carriers to producers is not yet known, the research has important implications. Preventing or eliminating opportunistic infections is not only essential to the immediate well-being of the patient, but can also slow the cycle of virus production that leads to further immune system damage.

Saliva

Of all the organs in the craniofacial-oral-dental complex, it is perhaps the salivary glands and their remarkable secretory product, saliva, that forge the strongest link between oral and systemic health. Salivary function is extremely sensitive to changes in our general well-being, ranging from subtle effects of over-the-counter cold medications to the devastation of life-threatening disease.
Even the ancients recognized an association between the human condition and saliva, which served as judge and jury in cases of wrong-doing. A suspect was given a mouthful of dry rice. If his anxiety reduced his saliva flow so that he could not swallow it, the verdict was guilty as charged. To this day, "cotton mouth" betrays all of us at some point in our lives, signaling to the world that our nerves have taken control.

Gatekeeper

With its vast antimicrobial arsenal, saliva represents a remarkable evolutionary selective advantage for the host against invading pathogens such as HIV, the fungus *Candida albicans* , and a host of bacteria associated with oral and systemic diseases. Secretory antibodies, for example, directed against viral pathogens such as poliovirus and cold viruses, as well as the anti-HIV agent SLPI, are found in saliva. Large salivary glycoproteins called mucins appear to have antiviral properties as do cystatins, a family of cysteine-rich proteins that are active against herpes viruses.
Saliva also contains histatins, anti-fungal proteins that are potent inhibitors of candida, which is normally kept in check at extremely low levels in the mouth. When the oral balance is upset, however, by HIV infection or other immunosuppressive and debilitating disorders, antifungal defenses are overwhelmed and candida flourishes uncontrolled.
Reinforcing saliva's antiviral and antifungal activity are salivary constituents that thwart bacterial attack. These enzymes destroy the opposition by various mechanisms, including degrading bacterial membranes, inhibiting the growth and metabolism of certain bacteria, and disrupting vital bacterial enzyme systems.
Functioning in concert, these and other protective factors in saliva help to maintain the oral environment in optimal working order and restore it to more normal conditions when disturbed. But protection of the oral tissues reflects only one dimension of this versatile fluid and its constituents. Research has found a new role for saliva as an effective laboratory tool.

New Diagnostics

Long known primarily for its protective and lubricating properties, saliva is now meeting the demand for inexpensive, noninvasive, and easy-to-use diagnostic aids for oral and systemic diseases, and for assessing risk behaviors such as tobacco and alcohol use. Detection of HIV by the presence of virus-specific antibodies in saliva, for example, has led to the development of commercially available test kits. These offer the sensitivity of a blood test, but without the discomfort of a needle stick.
The strong correlation between HIV antibodies in saliva and serum has spurred the use of saliva as a monitor for other viral antibodies and antigens. Experimental salivary assays have already been developed for detecting antibodies for measles, mumps and rubella. Saliva is also reliable in diagnosing viral hepatitis A, B

and C in laboratory tests.
As an investigational diagnostic aid and potential monitor of disease progression, saliva has been used increasingly in systemic disorders that affect salivary composition and gland function, including Alzheimer's disease, Sjögren's syndrome, cystic fibrosis, diabetes, and diseases of the adrenal cortex. Saliva is also proving to be an effective tool to monitor levels of hormones and therapeutic medications -- as well as the presence of illicit drugs.
Research opportunities abound to develop more sensitive and specific assays to measure and understand changes in saliva beyond oral and systemic diseases to areas such as genetic defects, nutritional status, and age-specific changes.

Salivary Gland Dysfunction

Although viewed as champions of the oral cavity, the salivary glands are not spared insult or disease. The parotid, submandibular, and sublingual glands that comprise the major salivary glands are directly affected by a variety of conditions, including infection (such as mumps), obstructions, developmental disorders, and tumors. Two major diseases, cystic fibrosis (CF) and Sjögren's syndrome, can devastate these vital glands.
In cystic fibrosis, a defect in chloride ion transport causes exocrine gland secretions, including saliva, to be thick and viscid and leads to chronic lung disease and pancreatic insufficiency. Studies of salivary acinar (salt and water secreting) cells, a convenient model for exploring mechanisms of chloride ion transport, have greatly expanded the understanding of exocrine gland transport systems in human salivary glands. The identification of the defective gene in cystic fibrosis has also led to clinical trials using gene therapy to treat this disorder.

Gene Transfer Technology

Applying the same technology used in the CF trials, scientists have successfully introduced human and bacterial genes into the salivary glands of rats. This advance holds potential not only for repairing diseased or damaged salivary glands, but also for enabling the glands to produce therapeutic drugs for delivery into the mouth.
The researchers used a common cold virus (adenovirus), altered to prevent reproduction, and packaged in it either human or bacterial genes that could make readily detectable proteins. When introduced through the salivary ducts, the genetically altered virus particles infected the ductal cells as well as the fluid-secreting acinar cells. The foreign genes then made their specific proteins that were detected inside the infected cells and in saliva secreted from the cells, confirming that this system of gene transfer can be used to make salivary tissues produce functional proteins.
This advance has already found application in animal studies that could eventually lead to a new treatment for thousands of people whose salivary glands are damaged by radiation therapy for head and neck cancer. While head and neck radiation treatment kills cancerous cells, it also often destroys vital acinar cells that lie within the radiation field. Patients are unable to produce adequate saliva, leading to a host of long-term problems including xerostomia (dry mouth), mucositis, rampant dental caries, infections of the mouth and pharynx, and difficulty with swallowing, speech and taste. These conditions dramatically reduce quality of life and can also be the source of systemic infections that may threaten patient survival or interfere with their cancer treatment.
NIDCR scientists have now tricked non-fluid producing ductal cells into making saliva. Unlike acinar cells, ductal cells frequently are not destroyed by irradiation. The researchers sought to genetically re-engineer ductal cells into fluid producers by giving them a gene for an aquaporin protein, a recently discovered family of proteins that form pores in cell membranes through which fluid can pass. They inserted an aquaporin gene into an altered adenovirus and then infected irradiated rat salivary glands with the virus. Remarkably, the ductal cells produced fluid.
Although human application is likely several years away, the NIDCR research team is optimistic about the potential use of gene-mediated therapeutics for restoring salivary gland function.

Sjögren's Syndrome

Eagerly awaiting clinical advances in salivary gene transfer are many thousands of people with Sjögren's syndrome (SS), an autoimmune disorder that primarily affects women. Classic symptoms include dry mouth, eyes and other mucosal surfaces, accompanied in about half the cases by a connective tissue disease such as rheumatoid arthritis or systemic lupus erythematosus. The oral dryness interferes with normal functions of talking, chewing and swallowing and, deprived of the protective properties of saliva, puts SS patients at high risk for dental and oral infections.
Investigators are looking closely at alterations in salivary gland function associated with Sjögren's syndrome.

Because salivary involvement in this disorder is highly variable, ranging from mild impairment to total loss of function, early diagnosis is difficult. Studies are aimed at defining criteria for early and unequivocal diagnosis and establishing clinically useful markers for salivary gland disease activity.
The inflammatory cytokine interleukin-6 (IL-6), for example, has been found at elevated levels in the saliva of SS patients and may serve as a marker for this disorder. IL-6 and other elevated cytokines are thought to play a significant role in the pathogenesis of Sjögren's syndrome; the mechanism, however, is unknown.
Research is also under way to develop a new noninvasive or minimally invasive means of diagnosing salivary gland involvement in SS using laser spectroscopy techniques. Currently, definitive diagnosis requires surgical removal of minor salivary glands. Laser spectroscopy to detect labeled cells specific to Sjögren's syndrome would not only obviate the need for surgery, but would also permit repeated testing of the salivary glands to follow the course of the disease and effectiveness of therapy.

Xerostomia

Another major source of dry mouth -- medication -- affects most of us at some time in our lives. More than 400 prescription and over-the-counter drugs are known to have xerostomic effects. Many of these medications are taken daily, particularly by older Americans, to treat chronic conditions such as hypertension and depression. Although salivary gland function does not normally decline with age, the oral dryness experienced by many older persons from certain diseases and long-term medications heightens their risk for oral and dental infections. As the population ages -- by 2010, 40 million Americans will be 65 or older -- vulnerability to an array of chronic and disabling disorders and the oral effects of medications prescribed for their management will present significant challenges to health care providers.

A New Research Tradition

The identification of dental caries and periodontal disease as infectious diseases by the 1960s heralded the first revolution in dental research. We are now in the midst of a second revolution where oral health research is taking its place in an ever-changing scientific world driven by the need to understand health and disease through the intricate interactions of human behavior, environment, and biology.
What is emerging is a biology of complexity as we approach the 21st century. Infectious diseases that took the young lives of our ancestors have been replaced with chronic and degenerative diseases that victimize us in our old age. These changing patterns of disease and demographics now challenge science to shift its focus from its success in extending life to the challenge of improving the quality of life from before birth until death. To reach this goal, science cannot look at a single molecule, or cell, or system in isolation, but rather at how these act in concert with behavioral, environmental, and genetic influences to heighten or minimize one's risk of disease.
Once the grist of science fiction, today a human genetic book is in process that will eventually decode each of the 100,000 genes that comprise the human genome. We now know that virtually all human diseases have a genetic component, including inherited, infectious, neoplastic, and chronic disabling craniofacial-oral-dental diseases and disorders. We are learning about inherited susceptibility genes that predispose to disorders such as diabetes and severe periodontitis, and we are finding that some chronic diseases may share major genetic determinants and, perhaps, diagnostic and therapeutic approaches as well.
The oral and systemic health connection, then, lies in the many factors they hold in common. Fully integrated into the realm of biomedical research, oral health science is not only expanding our understanding of craniofacial-oral-dental diseases and disorders, but also is broadening the critical knowledge base of fundamental disease processes.