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NIMH, NIH Scientists Track New Clues On Biological Basis of Stress, Depression

NIMH and NIH scientists have turned up new biological clues about how a key brain hormone may become hyperreactive in affective (emotional) disorder, precipitating a cascade of abnormal endocrine responses typically seen in depressed patients.

The findings suggest a new model for understanding how severe stresses early in life might lead to a permanent hyperreactivity to stress and mood disorder in vulnerable persons.

Drs. Philip Gold of NIMH and George Chrousos of the National Institute of Child Health and Human Development discussed such possible implications of their experiments with a recently purified neurohormone, CRF (Corticotropin Releasing Factor), at an NIH Science Writers' Seminar on the "Molecular Basis of Stress" recently.

The seminar, moderated by Dr. Frederick Goodwin, Director of the NIMH Intramural Research Program, also featured presentations by Drs. Julius Axelrod and Steven Paul, also of NIMH.

The scientists discussed new findings about how the body's stress response is mediated via the hypothalamic-pituitary-adrenal (HPA) axis.

The availability of synthetic CRF within the past year has spurred a new wave of studies on this HPA axis. Drs. Gold and Chrousos reported at the seminar on the first experiments using the hormone as a challenge drug in primates and humans.

When injected with the neurohormone CRF, depressed patients showed a lower response in their blood ACTH levels than did controls. Depressed patients commonly have abnormally elevated levels of cortisol in their blood.

When normal subjects received a continuous infusion of CRF, their blood cortisol levels showed a modest rise that mimicked the cortisol levels of many depressed patients. Growth hormone levels of depressed patients injected with CRF resembled those of similarly stressed primates. Both were elevated.

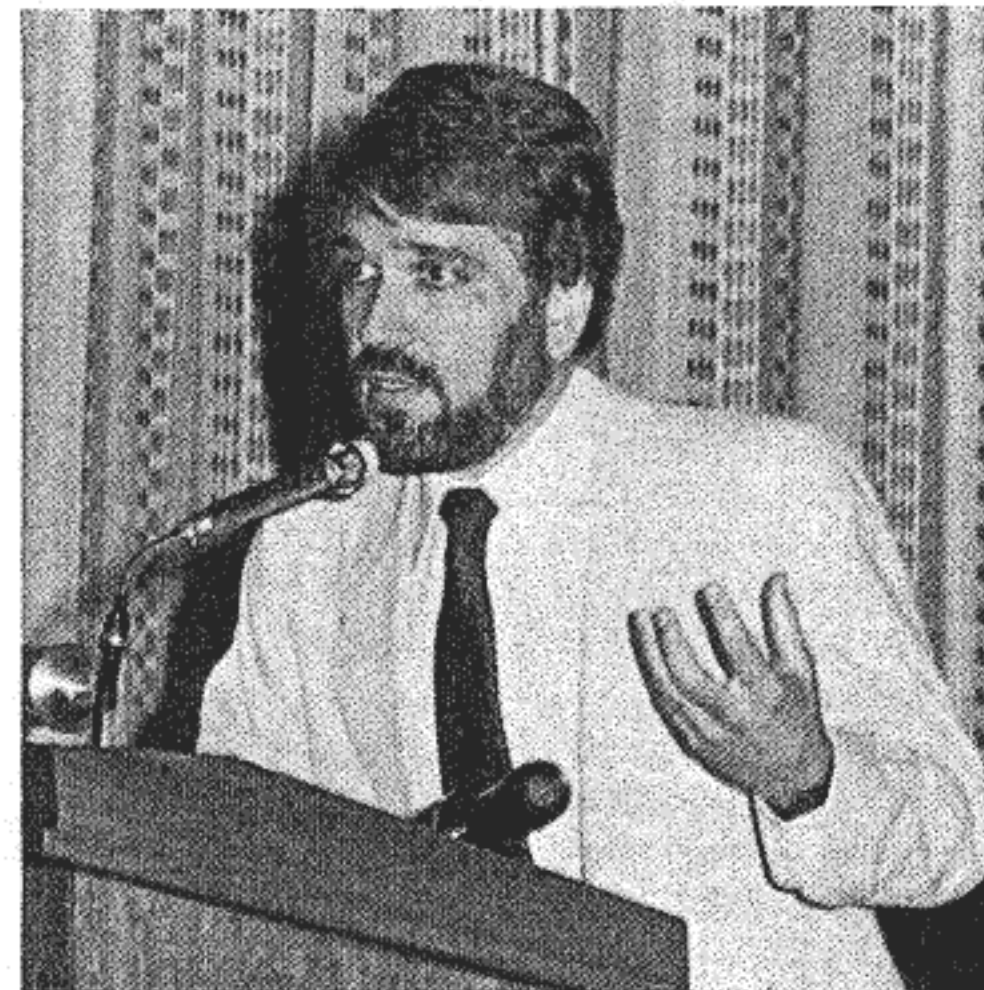
These findings suggest that depression involves an excess of CRF secretion, according to Drs. Gold and Chrousos.

A Theory of Depression

Dr. Gold offered what he cautioned was "simply a model" that early prolonged stressed might sensitize genetically vulnerable individuals to chronically oversecrete CRF and to hyperreact to stress and develop mood disorder later in life. As supporting evi-



Dr. Gold



Dr. Chrousos

dence, he pointed to a well-documented tendency among depressed patients to have a history of early stresses (particularly separations from parents and other loved ones) associated with intense anxiety, and to relieve these feelings repeatedly during stressful times.

In addition, Gold cited animal studies that found permanent rises in the reactivity of HPA axis hormones in response to stresses administered during early critical periods.

Gold suggested that since HPA activation and depressive symptomatology are not unique to primary depression, excessive CRF

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Second Cell Defect Found in AIDS Cases

A team of scientists, headed by Dr. Anthony S. Fauci, of the National Institute of Allergy and Infectious Diseases (NIAID), has found that patients with Acquired Immune Deficiency Syndrome (AIDS) have functional defects in both major classes of lymphocytes—T cells and B cells—that usually protect the body against disease.

Until now, investigators believed that the immune abnormalities in AIDS patients involved only the T cells, specifically a decrease in the helper/inducer subset of T cells. Among other functions, the helper/inducer cells normally work with the suppressor subset of T cells to regulate antibody production by B cells.

Dr. Fauci and his colleagues studied 12 homosexual men with AIDS, 5 healthy homosexual men, and 12 heterosexual controls.

As expected, the AIDS patients were deficient in helper/inducer T cells and had decreased helper-to-suppressor T-cell ratios.

In addition, when the subsets of T cells were studied separately in the laboratory, the scientists found the suppressor cells functioned normally, but the helper cells did not.

Further studies showed marked abnormalities in B-cell activation and regulation in the patients. Their B cells did not react to substances that ordinarily stimulate antibody production. Also, the patients had abnormally high numbers of B cells spontaneously secreting different kinds of antibodies (polyclonal activation).

This increase in activated B cells is similar to what occurs during certain viral infections, such as mononucleosis. In that case, the Epstein-Barr virus infects the B cell, which becomes transformed and begins spontaneously to secrete antibody. Infections with cytomegalovirus cause similar reactions.

Generally, after such infections, T-cell regulators step in to restore normal balance to the immune system. In the case of the AIDS patient, the defective helper/inducer T cells may fail to stimulate the suppressor cells to slow the abnormal B-cell activity.

Healthy homosexual men in this study also showed alterations in immune function when compared to the heterosexual control group.

Although, there were wide variations in the immune responses of the healthy homosexuals, the results generally fell between those of the AIDS patients and the heterosexual controls. What causes these alterations and how they relate to AIDS are still unknown.

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Dr. S. Kety, Renowned Psychiatric Researcher, Returns to NIMH After 16 years at Harvard

Seymour Kety, one of the senior statesmen of biological psychiatry, is returning to NIMH this month after a 16-year hiatus at Harvard. Among his first duties will be a job he first served in 27 years ago.

In 1956, Dr. Kety resigned as director of the NIMH Intramural Research Program (IRP) to become the first chief of its newly created Laboratory of Clinical Science. In mid-September, Dr. Kety again becomes chief of that same lab as well as IRP associate director for basic science.

Dr. Kety's homecoming adds a nostalgic twist to a scientific odyssey that has taken the 68-year-old investigator from pioneering probes of blood flow in the brain to landmark adoption studies of schizophrenia in Denmark.

The holder of 50 professional honors and mentor of a generation of psychiatric researchers, Dr. Kety is "the father of the modern era of biological psychiatry and its integration with the neurosciences," according to Dr. Frederick Goodwin, IRP director.

In 1951, Dr. Kety became the first scientific director of the then fledgling predecessor of the IRP (it was then a joint mental health/neurology program).

Convinced that few scientific discoveries result from attacking a problem "head-on"—particularly in such a new field as mental health—he designed the structure of the program's laboratories according to scientific disciplines (e.g., neurochemistry, psychology) rather than according to problem areas (e.g., schizophrenia, depression).

Good scientists flourish in the climate of freedom and continuity afforded by such "home bases" in their own respective traditions of inquiry, he reasoned.

Investigators could mount targeted, mission-oriented research on a more flexible basis as the field progressed. The legacy of labs established and scientific leaders recruited by Dr. Kety during those formative years lives on in today's IRP.

Some of his major contributions to developing mental health research actually resulted from studies with negative findings. "His emphasis on tight controls and high standards in clinical experimentation kept many young investigators from going off in directions that ultimately proved not to be fruitful," explained Dr. Goodwin.

AIDS

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Dr. Fauci stresses that the cause of AIDS remains a mystery. This study reveals B-cell abnormalities that are highly suggestive of viral stimulation in the absence of normal regulatory T-cell activity. More research is needed on the B-cell defects as well as on the T-cell dysfunction in AIDS patients.

This study was reported in the Aug. 25, 1983, issue of the *New England Journal of Medicine*. The authors are Drs. H. Clifford Lane, NIAID; Henry Masur, NIH Clinical Center; Lynn C. Edgar, and Gail Whalen, NIAID; Alain H. Rook, FDA; and Anthony S. Fauci, NIAID. □

The current IRP director also credits Dr. Kety with recognizing early the potential of using radioactive tracers to study brain mechanisms and facilitating use of this research strategy which underlies the Nobel prize-winning studies on catecholamines (epinephrine, norepinephrine, etc.) of Dr. Julius Axelrod, Dr. Louis Sokoloff's Lasker award-winning glucose mapping experiments, and such recent innovations as positron emission tomography.

Dr. Kety was the first investigator to perfect cerebral blood flow technology and apply it to the study of mental illness during the early 1950s. During a sabbatical in France during the 1960s, he conducted important experiments on stress and electroconvulsive therapy. His later adoption-and-twin studies of schizophrenia, conducted in Denmark, have been widely recognized as breakthroughs in understanding the role of genetics in that disorder.

Dr. Kety will serve as a principle advisor to Dr. Goodwin on matters of science policy, program management and research planning. He will also serve as a mentor to younger investigators and conduct his own research projects in neuropharmacology and models of schizophrenia. As interim chief, he will help restructure his old Laboratory of Clinical Science following Dr. Irwin Kopin's recent departure. □

AIDS Nursing Conference Set for October at NIH

AIDS (Acquired Immune Deficiency Syndrome) will be the subject of a national clinical nursing conference on Friday, Oct. 7. The conference, sponsored by the Clinical Center Nursing Department, will be held from 8 a.m. to 5 p.m. in the Masur Auditorium.

The conference is designed to provide nurses with information on current theories regarding the etiology and transmission of AIDS. Issues related to diagnosis, research protocols, and treatment will be explored. The psychosocial needs of patients, families, and health care workers will also be addressed.

The conference will be opened by Rena M. Murtha, associate director for nursing at the Clinical Center. Clinical Center nurses will also give presentations on topics such as "Nursing Diagnosis, Defining Characteristics and Care Plans for Ambulatory Care Patients," and "Psychosocial Needs of Patients."

Other speakers include Dr. Anthony Fauci, chief of NIAID's Laboratory of Immunoregulation—who has led the investigations on AIDS—as well as Dr. David K. Henderson, the Clinical Center's epidemiologist, and Dr. Henry Masur, deputy chief of the Clinical Center's Critical Care Medicine Department. Speakers from the Clinical Center Social Work Department, NINCDS, and NIMH will also join in the conference.

For further information, call 496-5661. The registration deadline is Sept. 16. □



NIH Merit Award Given To Five NIADDK Employees

Five NIADDK employees were recently honored with NIH Merit Awards by Dr. Lester B. Salans, NIADDK Director. (See picture.) These are: (front row, l to r) **Helen C. Jenerick**, secretary (Stenography), Division of Intramural Research, "for superlative performance as a secretary for the Laboratory of Biochemical Pharmacology, NIADDK"; **Rose Lee Claggett**, copier-duplication equipment operator, DIR, "for consistently superior performance in the Division of Intramural Research, NIADDK;" (back row, l to r) **Dr. David G. Badman**, Director, Hematology Program, Division of Kidney, Urologic and Hematologic Diseases, "in recognition of his superior administration of the Hematology Program, NIADDK, and his leadership of the study, Research Needs in Hematology;" **Dr. Sarah C. Kalsner**, Director, Liver and Biliary Diseases Program, Division of Digestive Diseases and Nutrition, "for her high level of leadership in directing and administering the Liver Diseases extramural program for the Institute" and **Dr. Walter S. Stolz**, Acting Director, Division of Extramural Affairs, "in recognition of major contributions to NIADDK which have exemplified the very highest standards of excellence in health science administration."

The NIH Merit Award is the second highest honor presented by NIH to Civil Service employees. It is designed to "recognize and acknowledge the work of some of the highly motivated and dedicated staff at NIH who have made worthy contributions toward the support of scientific research." □

Volunteers Needed

Volunteers are needed in health research, computer science, medical, education, arts/culture, counseling/guidance, recreation, public relations, environmental, and administrative/clerical programs in the Metropolitan area.

Call the Volunteer Clearinghouse nearest your home for an interview: Alexandria, 836-2176; Arlington, 558-2654; Washington, D.C., 638-2664; Fairfax, 691-3460; Montgomery, 279-1690; and Prince William, 369-5292. □