

The Newsletter of THE AMERICAN INSTITUTE OF STRESS

Number 11

1994

SEVENTH INTERNATIONAL MONTREUX CONGRESS ON STRESS

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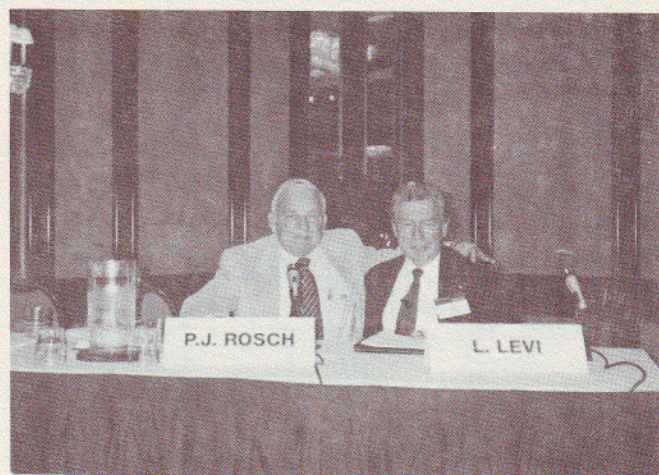
Plenary Sessions on Stress and Depression, The Evolution of Global and Coronary Prone Type A Behavior, Clinical Applications of Psychoneuroimmunology, International Labor Organization Survey of Job Stress Around the World, Advances in Occupational Health Promotion and Stress Management, Stress Reduction Effects of Subtle Electromagnetic Energies, Stress and Sleep, Stress, Neurotransmitter Disturbances, Antioxidants, and Aging, Eastern Stress Reduction Strategies. Presentation of Hans Selye Award to Ray H. Rosenman, M.D. Round Table Discussion with previous Hans Selye Award Recipients on "Stress and Quality of Life" (Stewart Wolf, Bjorn Folkow, Jim Henry, Yujiro Ikemi, Lennart Levi, Joel Elkes). Registration Limited.

FIRST WORLD CONGRESS ON STRESS

The First World Congress on Stress commenced at 4 p.m. on October 4, and concluded 72 hours later. Including posters, there were well over 300 presentations. Because of time constraints, the 65 papers delivered were limited to 20 minutes each, time could not be allotted for discussion, and evening sessions often lasted till 10:00 p.m. for the 500 enthusiastic registrants. The topics ranged from esoteric molecular biology research to broad psychosocial issues. Categorizing these to achieve cohesiveness and continuity for each of the sessions was a Herculean task. Drs. Kvetnansky, McCarty, Chrousos, and others should be congratulated for doing a superb job in this regard.

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C.B. Nemeroff, Editor (Book Review on last page)	



Drs. Paul J. Rosch, President of The American Institute of Stress, and Lennart Levi, Professor and Chair of the Department of Stress Research, Karolinska Institute, Chairpersons of PSYCHOSOCIAL ASPECTS OF STRESS.

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The Newsletter of
**THE AMERICAN INSTITUTE OF
 STRESS**

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The program was divided into ten Plenary Sessions, entitled:

- Hypothalamic-Pituitary-Adrenal Axis In Stress
- Basics Of The Stress Response
- Central And Peripheral Catecholamine Systems In Stress
- Stress-Related Neuroendocrine Systems
- Molecular Biology Of Components Of The Stress Response
- Stress And The Immune System
- Stress, Gender, Ontogenesis, And Aging
- Stress And Somatic Illness
- Psychosocial Aspects Of Stress
- Stress Related Psychiatric Illness

Dr. W. Vale of the Salk Institute delivered The Hans Selye Memorial Lecture, *Biological And Molecular Characterization Of CRH, Its Receptor And Binding Protein*, which was sponsored by the Hans Selye Foundation. (The appropriateness of this subject is underscored by the review of *Neuropeptides And Psychiatric Disorders*, which appears in this issue.) The agenda included a Dinner Reception on October 5, together with a Young Investigator Award Ceremony, (bestowed on Dr. L. Goldstein from Yale), and a Constituent Assembly For The Establishment Of A World Stress Society. This was deferred for the present.

The First World Congress on Stress was organized under the auspices of the National Institutes of Health, with particular representation from The National Institute of Child Health and Human Development, National Institute of Mental Health, National Heart, Lung, and Blood Institute, and Office of Alternative Medicine. It was presided over by Professor Graham Burrows of Australia, President of The International Society for the Investigation of Stress, another co-sponsor of this event. In addition, a number of pharmaceutical companies provided financial support as corporate sponsors. It would be impossible to adequately describe this meeting in the space available, but some flavor of what transpired may be gleaned from the subject matter of a few of the presentations.

- "Reflectance Imaging Of The Hypothalamic Paraventricular Region Demonstrates Biphasic Cellular Activation Patterns In Freely Behaving Cats During Noise Exposure."
- "Effect Of Neonatal Hippocampus And Amygdala Lesions On Sympatho-Adrenal System And Hypothalamic-Pituitary-Adrenal Axis Responsiveness To Immobilization In Rhesus Monkeys."
- "Responses To The 5-HT_{1A} Agonist Ipsapirone During Glucocorticoid Antagonism With Ketacanzole."
- "Accelerated Lipofuscin And Ceroidolysis By Meclofenoxate And Antagonistic-Stress In The Brain Tissue."
- "Arcuate Nucleus Neurons That Project To The Hypothalamic Paraventricular Nucleus: Neuropeptidergic Identity And Increased POMC And NPY mRNA Levels Following Long-Term (8 week) Antidepressant Drug Treatment"
- Repeated Stress Induces Chronic Fra's But Decreases c-Fos Expression In Specific Regions Of Rat Brains."
- "Role Of HSP72 In Protection Against Stress-Induced Alterations Of Tau Protein In Neurons."
- "The Influence Of Dalargin On Stress-Induced Alteration Of Immunity In Rats With Different Locomotor Activity."
- "Excitotoxic Amygdala Lesions Block Condition Stress-Induced Medial Prefrontal Cortical Dopaminergic, Serotonergic, And Noradrenergic Metabolic Activation: Behavioral, Neuroendocrine, And Neurochemical Studies In The Rat." (Dr. Goldstein)

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The clinical research reports also covered a wide variety of subject matter, as evidenced by:

- "Screening And Intervention System For Mental Work Stress"
- "Acute Confusional States In Alzheimer's Disease"
- "Psychophysiological Stress And Muscle Tension"
- "Towards An Understanding Of Pre-Menstrual Syndrome In Women"
- "Predicting The Mental Health Outcomes In Air Traffic Controllers: Impact Of The 1981 PATCO Strike"
- "Role Of Yogic Massage In Adaptive Dysfunction Of Cortico-Hypothalamic-Pituitary-Adrenal Axis In Stress"

There was a preponderance of basic research presentations, and because of time limitations, a variety of important clinical topics could not be addressed. In other meetings, this problem is avoided by holding simultaneous sessions dealing with either animal or human research. While this has certain advantages, in my opinion, it is counterproductive. The purpose of meetings such as these should be to encourage interdisciplinary cross fertilization and integration. The organizers should be congratulated in not taking this easy way out to solve their time constraints. However, I suspect that the clinicians could have gotten much more out of the basic research presentations, and vice versa, had there been an opportunity to provide a more integrative approach, as well as ample time for discussion.

There is undoubtedly a wealth of important information already in existence that would be of great interest and could benefit each of us. The tragedy is that much of it is hidden and sequestered in relatively inaccessible nooks and crannies. Alternatively, it is expressed in unfamiliar argot that hinders optimal appreciation of its implications or applications for seemingly unrelated areas. As Stewart Wolf wrote in a letter to me several years ago, "Often the use of language is not shared across disciplinary lines. The restriction in scope and the sharpening of focus required in certain highly specialized fields often leads to the idiosyncratic use of words amounting ultimately to a parochial jargon interpretable only to the initiated. Thus, a lush growth of technical esoterica obstructs synthesis and beclouds understanding in a fashion reminiscent of the Tower of Babel."

We have strived to avoid this by emphasizing an integrative synthesis at our annual Montreux Congresses. Some of the presentations at the Bethesda meeting were also excellent in this regard, a few random examples being: Nemeroff - *Neurohormones, Stress and Psychiatric Illness*, Hobson - *Sleep And Stress*, Chrousos - *Contemporary Stress Theory*, Sapolsky - *The Adrenocortical Stress-Response And Its Social And Personality Correlates Among Wild Baboons*, and Hitzig - *Combined Serotonin And Dopamine Agonists Alleviate Multiple Stress Related Immune Disorders: Clinical Observations*. The Proceedings of The First World Congress will be published by The New York Academy of Sciences, although unfortunately, the discussions will not be included.

A Second World Congress to be held in Australia is being planned for 1998, and a small group of us were invited by Graham Burrows to assist in the planning for this. It is clear that the concerns expressed above will be addressed, and that the focus will be on providing a greater balance and integration between clinical and basic research findings. This Newsletter reviews three presentations dealing with different aspects of the relationships between stress, cellular growth, and aging, that will hopefully illustrate the value of this approach.

Paul J. Rosch, M.D., F.A.C.P.
Editor



Members of the Organizing Committee for The Second World Congress On Stress (Australia, 1998).

From left to right, Drs. David Wheatley, Graham D. Burrows, Paul J. Rosch, Richard Kvetnansky, Lennart Levi, and George P. Chrousos.

Stress, Growth Factors, and Cancer

Nerve Growth Factor (NGF) is a term used to describe macromolecular substances which induce rapid and profuse nerve fiber outgrowth from various neurons. Interest in NGF originated when a mouse tumor implanted into a 3-day chick embryo, was subsequently found to be innervated by nerve fibers emanating from the adjacent spinal root ganglia of the host. It was postulated that the implanted tumor released some humoral factor that selectively promoted fiber outgrowth from sympathetic and sensory ganglia. This was confirmed by in vitro studies, and further investigation revealed that NGF appeared to particularly influence certain types of nerve cells during their early development, but could affect other targets, including mast cells. NGF has now been discovered in the venom of several species of poisonous snakes, and in such varied locations as mouse submandibular salivary gland, guinea pig prostate, and bull seminal fluid. The teleological or homeostatic significance of this is not clear.

The discovery of NGF led to the search for other peptide molecules that could selectively stimulate specific cells, and such growth factors for fibroblasts, as well as hematopoietic and epidermal cells, have now been identified. Similar substances are released by platelets as a result of trauma, and are postulated to promote wound healing. It has long been suspected that malignant cells produce analogous agents, such as angiogenesis growth factor, and alfa tumor growth factor, that stimulate the tumor's ability to proliferate and invade surrounding tissue. The epidermal growth factor receptor has certain characteristics suggesting that it is responsive to gene products known to produce certain types of sarcoma.

These observations may have important implications for our understanding of the mechanisms that modulate the local growth and metastatic spread of malignant tumors. As previously emphasized in the Newsletter, there is a considerable amount of clinical and experimental research indicating that stress can exert significant influences on the growth and spread of various malignancies. A variety of

putative neuroendocrine and immune system pathways have been identified in an effort to explain this. However, not much is known about the effects of stress on various growth factors. Since NGF is the best characterized of these, and can be measured with the greatest accuracy, evaluating its response to stress would seem to be the logical place to start.

Much of the early research in NGF was conducted by authors of this presentation over two decades ago. They have also previously reported that aggressive and dominant behavior in male mice was associated with increased NGF blood levels, as well as concentrations in the hypothalamus. However, this was not limited to, or the result of aggression per se. Blood concentrations of NGF were actually higher in mice who were experiencing submission and defeat, suggesting that psychological distress was an even more powerful trigger for NGF release. Is the NGF response to stress mediated by pituitary-adrenal axis activities, or is it triggered by other neuroendocrine influences?

To examine this further, NGF, ACTH, and cortisol blood levels were measured in 20-24 year old soldiers experiencing their first parachute jump from an aircraft. In addition to samples collected from soldiers who knew they were selected to jump, specimens were also obtained from a control group who were aware they would not be participating in the jump. Measurements were made the evening before the jump, and 20 minutes after landing. Compared to controls, NGF increased 84% pre-jump, and 107% post-jump. Levels of ACTH and cortisol were similar pre-jump, but increased post-jump. This implies that NGF secretion precedes these classical endocrine responses to stress, although one could argue that the time intervals selected might not have been optimal. Simultaneous catecholamine measurements would also have been of interest.

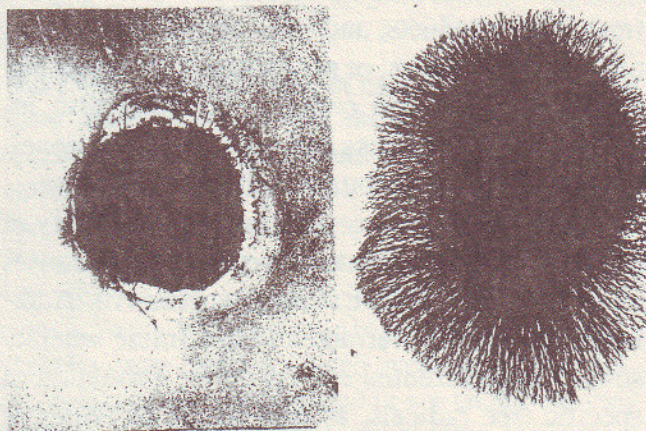
With respect to implications for malignant cell growth, in addition to neuroendocrine influences, stress can have powerful effects on immune system factors that may be particularly pertinent. Immunohistochemical analysis revealed that parachute jumping increased NGF receptors in circulating lymphocytes, both in pre-jump and post-jump measure-

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ments. This interesting observation suggests that the release of NGF following psychological stress may possibly activate certain immune system responses, which could have important clinical implications. It is not known whether other growth promoting factors respond to stress in a similar fashion, and this is clearly an area that warrants further investigation.

Based on **STRESS INDUCED BY PARACHUTE JUMPING ENHANCES BLOOD NGF LEVELS WHICH ARE NOT CORRELATED TO CORTISOL AND ACTH RELEASE**. Aloe, L., Bracci-Laudiero, L., Alleva, E., Tirassa, P., Lambiase, A., and Levi-Montalcini, R. (Presented at the First World Congress on Stress)



Photomicrographs of two sensory ganglia from an 8-day chick embryo in a medium without (left), and with (right), 10 ng/ml of the protein nerve growth factor.

“Mental Stress” and “Oxidative Stress”: Is There a Connection?

“Stress” has been used to signify or describe a wide variety of feelings and phenomena. These range from distressful emotions (anxiety, panic, and depression), and disturbing external events (stressors) such as the death of a loved one and physical trauma, to diverse pathologic consequences such as the development of a heart attack, peptic ulcer, or hypertension. In addition, centuries before Selye coined the term as it is commonly used, stress had been defined in physics as the external pressure

or force that produced strain, or deformation in any object. The strength of a material was measured in terms of its capacity to resist stress. Some materials were more resilient than others, and their elastic limit was the maximal stress that could be sustained, and still allow it to return to its original form. Hooke’s Law (1676) stated that within this elastic limit, strain was proportional to stress.

However, Selye had defined stress as the “non-specific **response** of the body to any demand for change”. Thus, he was clearly referring to a result, rather than a cause. He often complained that had he been aware of its use in physics, he would have gone down in history as the father of the ‘Strain’ concept. He subsequently had to create a new word, “stressor”, in an attempt to avoid the confusion he had created, especially when his research had to be translated into other languages. In addition to physics, stress is now also increasingly being used in biochemistry and molecular biology, one prominent example being “oxidative stress”. This refers to metabolic reactions in the body that consume oxygen, and particularly, excesses or abnormalities in these activities resulting from free radical actions.

In attempting to explain his concepts to a lay audience, Selye later redefined stress as “the rate of wear and tear on the body”. That also happens to be a fairly good definition of aging, at least from a biological, as opposed to a chronological perspective. Selye argued that this was more than a coincidence, since he had clearly demonstrated that various forms of chronic stress could accelerate the aging process in experimental animals. Stress not only significantly decreased their life span, but also produced premature macroscopic and microscopic changes characteristic of the manifestations of aging that did not develop in control litter mates until months later. It has now been fairly well established that most of these stigmata, including cataracts, gray hair, skin changes, atherosclerosis, and certain malignant changes, result from the ravages of oxidative stress. Indeed, “rust out”, might be a more appropriate description of aging than “wear out”.

In discussions of the influence of stress on aging, we use the term stress in its vernacular sense.

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Is There an Anti-Stress Medication to Prevent Fatigue and Aging?

The Spanish explorer, Ponce de Leon, thought he had found the "fountain of youth" in Florida, when he landed there in 1513. Since then, injections of monkey gland extracts by Brown-Sequard, Niehans' fetal cell therapy, and more recently, a genetically engineered version of natural growth hormone, have all had their enthusiastic supporters, because of alleged anti-aging attributes. Several decades ago, people flocked to Romania, because of reports that treatment with a procaine preparation developed by Anna Aslan, reversed graying of the hair and had other remarkable rejuvenative properties. Since stress seems to play such an important role in the aging process as well as many diseases, it would seem reasonable that if an anti-stress formulation could be concocted, it might improve longevity, as well as health.

Two reports from Romania propose that Antagonic-Stress (AS) is such a compound. It is described as "an anti-stress, anti-impairment, and anti-aging medication". In one double blind, randomized trial, AS was compared to placebo in 65-75 year old individuals with significant levels of psychosocial stress and age related impairments. Psychosocial stressors were judged to be moderate or severe (Axis IV of DSM-III-R), and impairment was minimal or mild as scored by the Sandoz Clinical Assessment Geriatric Scale. This multidimensional instrument has five subscales that measure cognitive, interpersonal, affective, apathy, and somatic components. Following three months of AS therapy, there was a decrease in all "psychogeriatric" measures. Mental and somatic "adaptive capacity", as well as "resistance level to stress" were increased, as reflected by improved cognitive, emotional, and coping responses.

In another report, the effects of AS and another drug, meclofenoxate, were studied in patients with "neurasthenia - fatigue syndrome". This is defined as a "neurotic stress related disorder highly correlated with stressful life style" and decreased pro-

ductivity. It is not clear whether this is the same as, or is related to, "chronic fatigue syndrome". Meclofenoxate is described as an anti-fatigue drug, and patients were treated with 1 gram daily. It may possibly be a congener of meclofenamate, a nonsteroidal anti-inflammatory pharmaceutical that has analgesic and antipyretic properties. The mechanism of action of meclofenamate is unknown, although it does not result from pituitary-adrenocortical stimulation, and may be related to inhibition of prostaglandin synthesis. The maximum FDA recommended dosage is 400 mg. daily, although toxicity is rare.

In this report, two groups of 55 people were treated for one month with either AS or meclofenoxate. Subjects were evaluated before and after treatment for cognitive performance (attention + memory), intelligence, and behavior, using standard, accepted instruments. Both of these medications "had important anti-stress and anti-fatigue actions". However, AS was judged to be superior, with respect to improving cognitive performance and behavior, and reducing the deleterious effects of stress on "intellectual efficiency". It was suggested that AS benefits are achieved by neurometabolic actions on the cerebral cortex, as well as the diencephalon and reticular formation.

It would be helpful to learn more about the composition of AS, and the background of its formulation. Many useful medications and therapies widely used in other countries are not available in the U.S., because of stringent FDA regulations. In some instances, there is no incentive to go through the expensive and time consuming process to obtain official approval, because there is no patent protection. On the other hand, this helps to insure the safety of such products, and to avoid potential disasters such as the thalidomide tragedy. We hope to learn more about AS at our forthcoming Montreux Congress in February.

Based on **ANTI-AGING AND ANTI-STRESS TREATMENTS IN ELDERLY PEOPLES**. G. Ionescu, S. Riga, D. Riga, N. Neicu and E. David and **NEUROMETABOLIC ANTI-STRESS INTERVENTION IN NEURASTHENIA**. G. Budileanu, S. Riga, and D. Riga. (Presented at the First World Congress on Stress)

Book Reviews • Meetings and Items of Interest

Book Review

Neuropeptides And Psychiatric Disorders, C.B. Nemeroff, Editor, American Psychiatric Press, Washington, 1991. 298 pgs. \$30.00.

This book is particularly timely in view of increasing efforts to establish objective criteria for the diagnosis and treatment of psychiatric disorders. Alterations in levels and relative ratios of specific brain neuropeptides provide a logical and practicable approach to this problem. For example, depression is more of a description than a diagnosis. Our ability to accurately predict prognosis or optimal therapy is based more on empiric observations and personal experience, rather than objective criteria. Many depressed patients have low serotonin levels, and drugs which inhibit CNS neuronal uptake of serotonin to improve this, are currently the most popular and effective forms of treatment. Transcranial electrical stimulation therapy for depression is most successful when it can be demonstrated to increase low serotonin levels. Other anti-depressant therapies, including monoamine oxidase inhibitors, tricyclic and tetracyclic drugs, lithium, ultraviolet light, electroconvulsive or insulin coma therapy, valproic acid, and other anticonvulsants, may act through other mechanisms involving melatonin, gamma-aminobutyric acid (GABA), inhibition of norepinephrine uptake, or by promoting electrical stability in the brain. Depression can be further classified by neuroendocrine distinctions, such as responses to thyrotropin releasing hormone, (TRH), dexamethasone suppression test, (DST), somatostatin, and thyroid autoantibody levels, etc. In particular, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, the premiere stress response pathway, has been demonstrated in many depressed patients, and levels of corticotropin-releasing factor (CRF) may be significantly elevated. Animals given CRF exhibit decreased appetite, sexual activity, sleep disturbances, and other behaviors commonly seen in depression. Recent studies suggest that exposure to stress early in life can have powerful effects on CRF neurons and their receptors. These and other observations may have important clinical implications, and could lead to novel pharmaceutical agents that act as CRF antagonists.

Over 60 brain neuropeptides have now been characterized, and there are undoubtedly hundreds or thousands more that may have clinical relevance. This concise volume provides specific chapters devoted to TRH, CRF, somatostatin, and anterior and posterior pituitary hormones, as well as neurotensin, cholecystokinin, neuropeptide Y (NPY), and endogenous opioids. In addition to their role in psychiatric disorders, they also modulate other stress related activities, such as pain perception, sleep, memory, mood, behavior, and disturbances in circadian and other biological rhythms. The discussions are particularly rewarding because of their ability to integrate basic research with relevant clinical observations. It is unfortunate that a chapter was not devoted to melatonin, and the usefulness of this volume, as well as some of the others in this splendid series could have been markedly enhanced by providing an index.

Meetings and Items of Interest

Dec. 5-11 The Psychology of Health, Immunity & Disease sponsored by The National Institute for the Clinical Application of Behavioral Medicine, Hilton Head Island, SC, call NICABM at (800) 743-2226

Dec. 7 Teenage Violence and its Implications for Schools, Families and Service Providers, Craig House Hospital, Beacon, NY call (800) 393-4440

Jan. 20-22 8th Annual Conference on Addictions, Florida Society of Addiction Medicine, Hotel Royal Plaza, Walt Disney World Village, Lake Buena Vista, FL, call (407) 627-6815

Feb. 1 Sleep Disorders, Queen's University Faculty of Medicine Office of CME, Holiday Inn, Kingston, Ontario, Canada, call (613) 545-2540 ext. 5113

Feb. 5-8 Cardiopulmonary Wellness and Rehabilitation, American College of Chest Physicians, Breckenridge, CO, call (708) 498-1400

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