

Endocrine news

MEMBER NEWS | PEDIATRIC HEALTH | Q&A

The “Congenital” Scientist

BY KELLY HORVATH | JAN 2023



Honored by both the Endocrine Society and the European Society of Endocrinology with the 2023 Transatlantic Alliance Award, George Chrousos, MD, ScD, has made significant contributions to endocrine research on both sides of the Atlantic! Endocrine News speaks with Chrousos about what this award means to him, conducting pioneering research on two different continents, the importance of studying stress, and why he became an endocrinologist in the first place.

In October, the Endocrine Society and the European Society of Endocrinology (ESE) jointly awarded the 2023 Transatlantic Alliance Award to Prof. George P. Chrousos, MD, ScD.

The Transatlantic Alliance Award, which began in 2021, recognizes a leader who has made significant advancements in endocrine research in Europe and the U.S. Chrousos, who is professor emeritus of pediatrics and endocrinology at the National and Kapodistrian University of Athens (NKUA) School of Medicine in Athens, Greece, as well as UNESCO Chair on Adolescent Health Care and director of the University Research Institute on Maternal and Child Health and Precision Medicine, both at NKUA, exemplifies transatlantic endocrine leadership.

Earlier in his career, Chrousos was chief of the Pediatric and Reproductive Endocrinology Branch at the National Institutes of Health (NIH)’s Eunice Kennedy Shriver National Institute of Child Health and Human Development and John Kluge Distinguished Chair in Technology and Society at the U.S. Library of Congress in Washington, D.C. His transnational training of more than 60 renowned physician-scientists coupled with his extensive research

contributions — he has written more than 1,000 original papers — make him a worthy recipient of this prestigious award. In 2014, he received the Endocrine Society’s Fred Conrad Koch Lifetime Achievement Laureate Award.

Chrousos has made outstanding and ongoing contributions to the endocrine community’s fundamental and clinical understanding of stress biology and medicine, the diseases of the hypothalamic–pituitary–adrenal (HPA) axis, and many stress-related disorders, including anxiety, depression, eating disorders, obesity, metabolic syndrome, sleep disorders, and inflammatory autoimmune and allergic diseases. He has even conceptualized and described new diseases: the chronic stress and inflammation syndrome (CSIS) and primary generalized glucocorticoid resistance, also known as Chrousos syndrome.

Chrousos’s achievements reflect a dual combination of outstanding basic and clinical creativity underscoring his standing as an international researcher and clinical leader of endocrinology and metabolism. *Endocrine News* is honored to have interviewed this luminary in the field.



Endocrine News: You are only the third recipient of the Transatlantic Alliance Award — that must be quite an honor. What does it mean to you?

George P. Chrousos: It certainly means a lot to me. It is a recognition of the biomedical research, teaching, and training work that I have done in both continents, the U.S. and Europe. I had the opportunity to mentor many physician-scientists and basic scientists, who now have top positions in academia, industry, and clinical practice in these continents and beyond.

EN: To have led two teams of physician-scientists both in the U.S. and in Europe is a remarkable accomplishment. What drives you?

GC: I am a “congenital” scientist and teacher. I enjoy biomedical research (i.e., the production of new knowledge), and I get a lot of satisfaction out of teaching younger colleagues the scientific method. I also appreciate the success of my trainees and see them as a projection of myself into the future.

EN: You are presenting “The Endocrine Basis and Implications of Stress and Its Management” at **ENDO 2023** — can you explain briefly what this research has uncovered?

GC: When I started my scientific career in the late 70s, the term “stress” was almost prohibited to use in the scientific literature (for various reasons). However, studying glucocorticoids, their molecular and cellular actions, the regulation of their secretion, and their effects in experimental animals and humans made it apparent to me that stress represents a major concept, as it plays key roles in both physiology and pathophysiology. After I reviewed the seminal work of two great endocrinologists, Walter Cannon and Hans Selye, on stress, I proceeded to clearly define stress as “the state of threatened homeostasis,” and to distinguish it both from “disturbing stimuli,” or “stressors,” and from “the adaptive response or stress response” of the organism.

Then, it became clear that the adaptive response is subserved by a heuristic “stress system,” whose proper function during stress is beneficial in the maintenance of homeostasis. This system’s response during stress, however, is beneficial only within certain activity and temporal limits and becomes

detrimental when it goes outside these limits. (This concept fully complies with the Aristotelian principle that “the good lies between two evils, too little or too much”!) Indeed, a tremendous amount of pathology results from the “adaptive response” to stress, when this response becomes “maladaptive” (i.e., pathogenic). In fact, the detriment to the organism when these limits are not respected is mediated by the actual mediators of the stress system, with the main ones being the glucocorticoids (i.e., cortisol in humans) and the catecholamines.

“I am a generalist at heart, and endocrinology, with its cybernetic roles involved in every bodily function, is ideal for me. Also, it is a very “scientific” field with both a clinical and a laboratory component, while its key involvement in homeostasis and stress gives it ancient philosophical roots and a glorious history.” – George P. Chrousos, MD, ScD, professor emeritus, pediatrics and endocrinology; UNESCO Chair on Adolescent Health Care; director, University Research Institute on Maternal and Child Health and Precision Medicine; National and Kapodistrian University of Athens (NKUA) School of Medicine, Athens, Greece



EN: How did stress become a major area of interest for you?

GC: As I was working with the rare but scientifically very interesting Cushing syndrome, it became apparent to me that the entire clinical picture of this condition, including its psychologic, phenotypic, cardiometabolic, and immune manifestations, were quite reminiscent of the clinical picture of many middle-aged people of both sexes, for some of whom, for obvious reasons, we reserve the term “pseudo-cushing.” At that time, corticotropin-releasing hormone (CRH) was isolated by W. Vale, and the 41–amino acid peptide became available for studies.

Several experiments performed by us and other groups demonstrated that intra-cerebro-ventricular administration of this stress mediator completely

reproduced the phenomenology of the stress response, including not only HPA axis stimulation, but also activation of the locus caeruleus–norepinephrine/autonomic nervous system. When I realized the central role of the stress system in physiology and pathophysiology, stress really became my guide and main research focus. Now I have concluded that all the so-called “chronic noncommunicable disorders,” including anxiety, depression, obesity, the cardiometabolic syndrome, diabetes mellitus type 2, allergic and autoimmune diseases, the psychosomatic disorders, etc., are, to a great extent, the result of chronic psycho-socio-economic stress. The latter is ubiquitous in modern societies.

When I became a senior investigator at the NIH, a young psychiatrist from the National Institute of Mental Health (NIMH), Philip W. Gold, came to work with me. He became my long-term collaborator and friend and introduced me into psychiatry and the main disorders studied at his institute at the time, mainly anxiety, major depression, and the eating disorders anorexia and bulimia nervosa, all of which we now know are strongly related to stress. His team and mine then started a major long-term collaboration that resulted in a strong “infusion” of endocrinology and, to some extent, immunology, into psychiatry, a collaboration that resulted in the elucidation of pathogenetic mechanisms in a series of psychiatric disorders, including the so-called melancholic and atypical depression.

A little after Philip Gold, another psychiatrist with expertise in sleep disorders, Alexander Vgontzas, from the University of Pennsylvania at Hershey, joined me for collaborative research on sleep. He also became a long-term collaborator and friend. A series of studies were undertaken that represented a strong “infusion” of endocrinology and immunology into sleep physiology and pathophysiology, with the elucidation of many pathogenetic mechanisms in sleep apnea, disorders of daytime sleepiness and fatigue, idiopathic insomnia, etc.

At about the same time, two rheumatologists/immunologists, Ronald Wilder and Esther Sternberg from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), collaborated with me in immunological projects, including the study of the Lewis rat model of “global” inflammation, and such diseases as rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, and so on, again with interesting endocrine results, with hypocortisolism being a common key factor in the expression of these autoimmune and allergic disorders (e.g., including fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis, asthma, etc.). Interestingly, hypocortisolism also characterizes the recently described long-COVID syndrome.

EN: What other topics are foci of your research?

GC: I started my research career with the study of the HPA axis, both its molecular and cellular biology and physiology, and the diseases related to it, such as glucocorticoid resistance and hypersensitivity, Cushing syndrome and Addison disease, congenital adrenal hyperplasia, polycystic ovary syndrome, premature adrenarche, and premature and delayed puberty. In the context of my clinical work, I continue to have an interest in and study these diseases and states to this day.

“Research advances in endocrinology are rapid, novel, consequential, and very exciting. Novel hormones and mechanisms are being discovered almost every week, and it will not be long before we solve clinical problems that today we consider unsolvable. Obesity, type 1 diabetes mellitus, endocrine tumors, cardiometabolic problems, etc., will become the past.” – George P. Chrousos, MD, ScD, professor emeritus, pediatrics and endocrinology; UNESCO Chair on Adolescent Health Care; director, University Research Institute on Maternal and Child Health and Precision Medicine; National and Kapodistrian University of Athens (NKUA) School of Medicine, Athens, Greece



EN: Do any specific papers among your 1,000+ stand out to you as favorites or especially important?

GC: Of course, some papers stand out. Especially those that represent the synthesis of my work regarding “[Glucocorticoids, tissue sensitivity, and disease](#)[KH1]” (*Annals of Internal Medicine*), “[Stress and health and disease](#)[KH2]” (*JAMA, Nature Endo Rev, Mol Psychiatry*), “[Stress and immune function](#)[KH3]” (*N Eng J Med, Annals of Internal Med*), “[Stress and reproductive functi](#)[KH4] on” (*Annals of Internal Medicine*), etc.

EN: What are you currently working on?

GC: Based on my work on the interaction of the [Clock-BMAL1](#)[KH5] heterodimer of our biological circadian clock with the glucocorticoid receptor, which suggested that evening cortisol elevations — as they occur in chronic stress, major depression, Cushing syndrome, night shift work, or traveling across time zones — are more detrimental to brain and cardiometabolic functions than morning elevations, my colleagues and I performed a very large epidemiologic study, which continues to this day, in which the so-called “medically unexplainable symptoms” (MUS) correlated well with body composition parameters, such as visceral fat and sarcopenia, morning plasma hsCRP and interleukin-6 levels, and loss of salivary cortisol circadian rhythm, with increased evening cortisol elevations. These data suggested that starting from the pediatric age range, chronic stress and stress-related “para-inflammation” gradually alter body composition and cause a cluster of absolutely explainable psychologic and physical manifestations, including MUS. These manifestations should be collectively called “chronic stress and inflammation syndrome,” or “CSIS,” which is ubiquitous and affects more than two thirds of middle-aged people. My current work extends the study of this syndrome, by examining how brain networks, especially those residing in the frontal cortex, participate in its genesis and on ways to prevent its development and to reverse its course.

My colleagues and I also study children conceived by assisted reproductive technology (ART), both by classic *in vitro* fertilization (IVF) and

[intracytoplasmic sperm injection \(ICSI\)](#).[\[KH6\]](#) We have shown that they have an increased risk of developing “(dys)metabolic syndrome” by blood biochemistry and by metabolomic and proteomic evaluations. We also study women with gestational diabetes and determine prognostic biomarkers of the pregnancy outcome. I am also involved in several large multicenter, multinational studies on pregnancy, gestational weight gain, and pregnancy outcome. In addition, I participate in studies on the healthy nutrition and growth of European children and adolescents.

[In the context of glucocorticoid resistance](#).[\[KH7\]](#) we isolated a long noncoding RNA called *Gas5* that interacts with the glucocorticoid receptor and prevents it from interacting with glucocorticoid response elements in the cell nucleus. This RNA is expressed in starving cells and protects them from the catabolic actions of glucocorticoids. Interestingly, the same RNA, along with many others, is expressed in exosomes of human milk. Currently, we examine the ability of these exosomal RNAs to enter the infant systemic circulation via breastfeeding. This likely represents horizontal epigenetic transmission.

EN: What led you to become an endocrinologist?

GC: I am a generalist at heart, and endocrinology, with its cybernetic roles involved in every bodily function, is ideal for me. Also, it is a very “scientific” field with both a clinical and a laboratory component, while its key involvement in homeostasis and stress gives it ancient philosophical roots and a glorious history.

EN: What is especially exciting in the field of endocrinology today? In medical research in general?

GC: Research advances in endocrinology are rapid, novel, consequential, and very exciting. Novel hormones and mechanisms are being discovered almost every week, and it will not be long before we solve clinical problems that today we consider unsolvable. Obesity, type 1 diabetes mellitus, endocrine tumors, cardiometabolic problems, etc., will become the past. In general, biomedical research, on the other hand, mental health, and cancer mechanisms are being gradually deciphered and understood, and I believe curative treatments are not far in the future, I can see them coming.

“I am a “congenital” scientist and teacher. I enjoy biomedical research (i.e., the production of new knowledge), and I get a lot of satisfaction out of teaching younger colleagues the scientific method. I also appreciate the success of my trainees and see them as a projection of myself into the future.” – George P. Chrousos, MD, ScD, professor emeritus, pediatrics and endocrinology; UNESCO Chair on Adolescent Health Care; director, University Research Institute on Maternal and Child Health and Precision Medicine; National and Kapodistrian University of Athens (NKUA) School of Medicine, Athens, Greece



© 2015 Copyright Endocrine Society. All rights reserved. 2055 L Street NW, Suite 600 | Washington, DC 20036

Phone: 202.971.3636 | Toll-free: 888.363.6274

Website Design and Development by **Matrix Group International**



Chrousos will present his award lecture, “The Endocrine Basis and Implications of Stress and Its Management,” at **ENDO 2023**, which will take place from June 15 to 18 in Chicago, Ill. Chrousos also will speak at ECE, the 25th European Congress of Endocrinology in Istanbul, Turkey, May 13-16, 2023.

Horvath is a freelance writer based in Baltimore, Md. She compiled and wrote the annual Eureka! feature in the December issue.
