A Neurologist with a Lifetime Fascination for Neurochemistry: Preface for the Special Issue Dedicated to Dr. Andreas Plaitakis

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It is a special privilege for us to write this preface in the special issue dedicated to Dr. Andreas Plaitakis, who has devoted his life both to neuroscience research and clinical neurology. It is hard to summarize his achievements in a few lines. However, one can say that the big loves of his life (apart from his daughters Ariadne and Iris, his granddaughter Sophia and his wife Oana-Cristina) are Crete,

Kassos, New York, tennis and glutamate dehydrogenase (GDH).

Andreas Plaitakis was born and grew up in Crete, during the hard period that immediately followed World-War II. He attended the Medical School of the University of Athens. He graduated in 1968, during troubled times for Greece. Then, after a compulsory military service of two years, he was assigned by the Ministry of Health of Greece to serve as the only physician on the island of Kassos (1970–1972), which belongs to the Dodecanese group of islands in South-East Greece. In this small and isolated island, he had to practice front line medicine without having the security provided by a nearby hospital. He quickly organized and run a Health Station that included electrocardiographic equipment, a small clinical laboratory equipped with state of the art coulter counter and a

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multi-chemistry analyzer and emergency surgical gear. In recognition of his dedicated efforts to improve the medical care on the island he was made Honorary Citizen of Kassos Island by the Local Municipality. Also, the Kassian Benevolent Association of New York has presented him with two Special Recognition Awards.

In 1972 he crossed the Atlantic and moved to New York, where he started his medical Internship at Long Island College Hospital in Brooklyn. One year later he began his residency in Medicine and later on in Neurology at the Mount-Sinai Hospital in Manhattan. Following his residency in Neurology and his NIH post-doctoral fellowship in Neurochemistry at the Laboratory of Dr. Soll Berl, he joined the Neurology Faculty raising through the ranks to become full Professor. Although he had tenure at the Mount Sinai School of Medicine, he decided to move from New York to Crete in 1996 to contribute as full-time faculty member to the development of the newly founded Medical School there. He was instrumental, along with other faculty members, in priming the School into adopting high academic standards and in establishing rigorous criteria for the appointment and promotion of its faculty, which were later on adopted by other Medical Schools of Greece. These efforts proved successful, as acknowledged in the 2010 External Evaluation report of the Medical School of Crete by an international panel of distinguished scientists: "...the School's strategy of attracting academics with strong research achievements have put it in a leading position nationally and in a competitive position internationally...". This was not an easy undertaking, however, as the novel ideas had to overcome the resistance of the established order. The ensuing clash was vividly conveyed in "The (faculty) Elections", a Cretan epic poem by Orestes Manousos, also a faculty member at the University of Crete, Medical School.

At the University of Crete he served as Professor and Chairman of Neurology of the Medical School of Crete and Director of the Neurology Department of the University Hospital of Heraklion, Crete. Also, for a decade he served as Director of the Graduate Program in Neuroscience of the University of Crete and Director of the Post-Graduate Studies of the Medical School. Presently, he is Professor Emeritus at the University of Crete, Medical School and Adjunct Professor at Mount Sinai School of Medicine in New York.

Dr. Plaitakis has focused his research interests on the molecular and cellular mechanisms underlying neurodegenerative diseases. His laboratory, initially in New York and later in Crete, cloned and characterized human proteins involved in the metabolism and transport of glutamate. His original observations on glutamate abnormalities in patients with degenerative neurologic disorders (Plaitakis et al., Science, 1982) opened a new chapter in

neurochemical research by linking a metabolic defect to mechanisms of excitotoxicity (Coyle, Trends in Neuroscience, 1982). His studies on glutamate alterations in Amyotrophic Lateral Sclerosis contributed to the development of riluzole (a glutamate-modifying agent) as the only effective treatment that is currently available for this devastating disorder. Due to his interest in the potential role of mitochondrial dysfunction in human degenerations, he focused his research on human GDH, a mitochondrial enzyme central to glutamate metabolism. Although the existing dogma at that time called for a single mammalian GDH, his laboratory in New York originally detected two distinct isoforms of human GDH; these efforts eventually led to the cloning of the human *GLUD1* and *GLUD2* genes that encode these proteins (see Shashidhran's contribution in this issue).

Research work in Crete uncovered the molecular mechanisms by which the newly discovered hGDH2 iso-enzyme acquired its unique properties. These efforts identified the evolutionary amino acid replacements responsible for new functional abilities adapted to conditions that prevail in the nervous and other systems. This work contributed to understanding the evolutionary steps by which the functional adaptation of the *GLUD2* gene was achieved, driven by positive selection, a process that may have played a role in human brain development (Burki and Kaessmann, Nature Genetics, 2004). Although hGDH1 and hGDH2 are highly homologous, the laboratory in Crete has successfully developed antibodies that can detect each of them specifically and used these antibodies to study the cellular distribution of the GDH isozymes in human tissues, thus uncovering clues for novel functions of these proteins. Also, his group originally reported that a gain-of-function variation in hGDH2 accelerates the commencement of Parkinson's disease onset and have identified compounds capable of selectively inhibiting the overactive hGDH2 enzyme.

Although GDH was the main research focus of his group, additional research interests during these years in Crete were the treatment of cerebral vascular accidents and the study of environmental and other factors that contribute to the pathogenesis of Multiple Sclerosis. He also studied the origin and mode of expansion of the (CAG) repeat in Huntington's disease families from Crete, as well as the epidemiology of Creutzfeldt–Jacob disease on the island. Dr. Plaitakis also maintains an interest in classic studies, particularly those that trace the origin of rational thinking and the use of scientific methods for approaching issues of health and disease. Together with Dr. Roger Duvoisin he published in 1983 a scholar paper revealing the existence in Homeric times of empirical knowledge that the flower *galanthus* ("snow drop") can counteract amnesia and behavioral changes induced by medicinal plants containing

anti-cholinergic agents and proposed a role for galanthamine (a cholinesterase inhibitor contained in *galanthus nivalis*) in modern neuro-pharmacology. Since then, galanthamine (also called galantamine) has been developed as an effective treatment for memory defects caused by Alzheimer's disease and other dementias.

Apart from research, Dr. Plaitakis has devoted much of his time to treating neurologic patients. In New York he worked as attending in the general Neurology ward, the Clinical Research Center, the Neurology Consultation Service and the Neurology Out-patient Clinics of the Department of Neurology at Mount Sinai Hospital (1979–1996). During this time, in addition to general neurology, he developed a special interest in ataxias, motor neuron diseases and movement disorders. His contribution to delivering a high standard neurology care along with teaching has been recognized by the Neurology Residents of Mount Sinai Hospital (Excellence in Teaching Award for the year 1994).

At the University Hospital of Crete (1996–2011) he established, organized and developed a new 30-bed in-patient Neurology Service, including a four-bed Acute Stroke Unit. He also organized outpatient Clinics for general Neurology and for Movement Disorders, Dementia, Multiple Sclerosis, Epilepsy, Neuromuscular Disorders, Stroke and Headaches. These activities upgraded the

delivery of Neurologic care to the population of Crete and generally in Greece, as recognized in the Evaluation of the Medical School and of the University Hospital of Crete (2008). He served for many years (1998–2013) as president of the Association for Research and Treatment of Neurologic Disorders of Crete EY ZHN, which is a non-profit organization that provides research fellowships to graduate and postgraduate students in Neuroscience and research grants for investigating the neurobiology of human neurodegenerations.

As Director of the Neurology Residency Program and the Graduate Program in Neuroscience at the University of Crete, he organized a Program that trained physicians-scientists (M.D., Ph.D), who could master both the Clinical and the Basic Neurological Sciences. This Program has trained young scientists, several of which have followed academic carriers in Europe and USA. It has served as a model for training neurologists and neuroscientists who can provide high level care to neurologic patients and at the same time perform ground breaking research. On behalf of his many patients, students, and fellow scientists, we have to thank him for his efforts all these years. For us, he has been model of an excellent clinician that can also excel in basic research.

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