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OBITUARY

Franz Halberg, MD (5 July 1919–9 June 2013) – In Appreciation

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FIGURE 1. Franz Halberg (1919–2013).

On Sunday morning June 9, 2013, one of the greatest scientists of the 20th and 21st centuries left us. His close associates also lost a very staunch friend and a mentor who never ceased to inspire. Franz Halberg's passing shy of his 94th birthday leaves a void that cannot be filled.

Franz Halberg (Figure 1) will be remembered for founding the fields of quantitative chronobiology, chronomics, and chronobioethics. These new transdisciplinary scientific disciplines could not have flourished without Franz Halberg's unveiling of lawful variations as a function of TIME within the physiological range and his vision that they had far-reaching implications. Toward this goal, he not only gathered a critical mass of data himself, but with a steadily increasing network of colleagues worldwide, he also developed inferential statistical methods for their analysis and interpretation.

By adding TIME to the existing body of knowledge in all of biology and medicine, and by recognizing the crucial role this new element plays in all matters of life, Franz Halberg developed the new science of chronobiology. By insisting on an inferential statistical foundation, details of a rich time structure were revealed akin to the finer spatial resolution obtained with a microscope. His methodical scrutiny of periodicities shared between biological systems and their broad environment, seen (photic) and unseen (non-photic) influences from the Sun and the cosmos led to chronomics in a way reminiscent of discoveries enabled by the advent of the telescope.

Franz Halberg was born on July 5, 1919 in Bistritz, Romania, where he received his elementary and secondary schooling. In 1943, he received his medical degree from the University of Cluj in Koloszvar. He became a citizen of Austria and worked in the Department of Anatomy at the University of Innsbruck from 1946 to 1948, first as a Scientific Assistant and later as a University Assistant. There, Franz studied the adrenal. In 1948, he immigrated to the United States, where he continued this work at Harvard Medical School with a World Health Organization fellowship in clinical endocrinology. He also held a position of Assistant in Medicine at the Peter Bent Brigham Hospital in Boston. In 1949, he joined the staff at the University of Minnesota Medical School, which saw his breakthrough experiments that led to the important discovery that circadian rhythms are partly endogenous and can be manipulated by environmental synchronizers, notably the lighting and feeding schedules. Franz coined the term circadian, after documenting that biologic rhythms tip the scale between health and

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disease and even between life and death. His results were widely published, including a 1969 citation classic (Halberg, 1969). By 1958, Franz had recognized the important role played by the cell's RNA and DNA cycles, which he was first to demonstrate as complementing the hypothalamic–pituitary–adrenal system as mediator of photic inputs. He subsequently added pineal feedsidewards and the understanding that there are endogenous physiologic networks that respond to the cosmos.

Beyond circadians, Franz demonstrated that many other built-in cycles resonate in part with their counterparts in our broad environment. His recent work focused on building a growing edifice of shared periodicities with bridges across disciplines. Wide-ranging applications were thus addressed, from the optimization of individualized health care to concerns for the health of societies. Franz strived to understand how to enhance positive thoughts and emotions as a scaffold for tolerance and love by seeking optimal configurations of the time structured realm of the mind, what he called the chronousphere. He was a scholar in the true sense of the word, combining science, philosophy, poetry, and spirituality, laying the foundation of chronobioethics.

With applications in all fields of medicine and biology, Franz's legacy is far-reaching. He will be remembered for his work in cancer chronotherapy. He showed that timing cancer treatment according to marker rhythms improves outcomes both in terms of heightened efficacy and lesser undesired side effects. Franz showed that a calorie is different whether it is consumed at breakfast or dinner. His principle of ''Primum nil nocere'' (above all, do no harm) prompted Franz to advocate the individualization of treatment, guided by marker rhythms, with important applications in preventive cardiology. By screening for abnormal patterns of blood pressure variability, appropriate circadian timed treatment more than halved the risk of stroke and other adverse cardiovascular events.

To many scientists, Franz Halberg is regarded as the father of modern chronobiology and its undisputed leader, particularly as it relates to biomedical research and therapy (Pauly & Scheving, 1987). Numerous scientists trained in his laboratory over the years, including many senior investigators and leading chronobiologists, including Dr Erhard Haus, who unexpectedly passed away on June 14, 2013, just a few days after Franz. Franz Halberg served for more than 10 years as President of the International Society for the Study of Biological Rhythms, and, after the Society's name was changed in 1971 at its meeting in Little Rock, Arkansas, he continued to serve as President of the International Society for Chronobiology (ISC) for another 15 years (Pauly & Scheving, 1987). Franz also served as Editor-in-Chief of the journal Chronobiologia, which published between 1974 and 1994, then served as the official journal of the ISC. In its first volume, Franz paid tribute to Arthur Jores for his pioneering interest in chronobiological topics several decades before they came to the forefront (Halberg & Engel, 1974; see also Jores, 1975), while he invited Hans Kalmus to recount the Foundation Meeting of the International Society for (the Study of) Biological Rhythms (Kalmus, 1974). To the historical perspective of the early development of chronobiology offered by Cambrosio & Keating (1983) and in a special edition of the Bulletin du Groupe d'Etude des Rythmes biologiques edited by Jean De Prins (1989), Franz summarized his life's work in two biographical records (Halberg et al., 2003, 2012), while his contributions to the chronomics of nutrition (Cornelissen, 2012) offer additional insight to the Minnesotan beginnings of the science.

Franz's lifetime accomplishments are summarized in his over 3500 scientific publications, in cooperation with colleagues from around the world. Many worldwide indeed call him their mentor and turned to him for advice, from study design and data analysis to the interpretation of results in the time dimension. Minnesota Medicine called him ''Father Time'', and colleagues in Russia and Azerbaijan honored him as ''Lord of Time''.

Franz's endeavors earned him numerous awards. Apart from holding professorships in Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral Medicine at the University of Minnesota, he was a Fellow of the New York Academy of Science and of the American Association for the Advancement of Science. Franz was a honorary member of the Romanian Academies of Science and Medical Sciences. He was also elected Corresponding Member of the French National Academy of Medicine. His Chronobiology Laboratories were officially affiliated with the University of L'Aquila in L'Aquila (Italy), the René Descartes University in Paris (France), and the Faculty of Computer Science at the Autonomous University in Madrid (Spain). Franz received medals from the University of Montpellier (France), the University of Krakow (Poland), the University of Ferrara (Italy), the University of Szeged (Hungary), and the Therapeutic Society of Moscow (Russia). Franz also received honorary doctorates from the University of Montpellier (France), Ferrara (Italy), Tyumen (Siberia), Brno (Czech Republic), L'Aquila (Italy), and People's Friendship University of Russia (Moscow, Russia). Franz was awarded the prestigious Arnold-Lucius-Gesell Prize from the Theodor-Hellbrügge Foundation. He was an elected member of the prestigious Leibniz Society and of the International Academy of Science. His achievements in the new field of chronomics earned him the O.Yu. Schmidt Medal and diploma for outstanding merits in development of geophysics, the first such award given to a non-physicist.

Until his last breath, Franz strived to introduce timing for diagnosis, prognosis, treatment, and first and

foremost prevention into clinical practice. At over 93 years of age and still active 7 days a week in the Halberg Chronobiology Center at the University of Minnesota, which continues his work, he was one of the last two recipients of a lifetime career award from the National Institutes of Health. The impact Franz had in science stemmed not only from his original findings but primarily from his vision of their implications that led beyond a scientific breakthrough to a new way of thinking. Franz's incredible persistence and intellectual clarity in the face of entrenched thinking in fields that transcend disciplinary boundaries sets him apart as a truly great scientist. As we say farewell with a great sense of loss, we remember Franz Halberg as a trail blazer who leaves a remarkable legacy that will live forever.

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