

In Remembrance: Franz Halberg, MD. (5 July 1919 – 9 June 2013)

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Franz often said he hoped he would leave the world a better place than he found it. He certainly did!

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 chronobiology (Halberg, 1969), chronomics (Halberg *et al.* 2001c) and chronobioethics (Halberg *et al.* 2012b). 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



Fig. 1. Franz Halberg (1919-2013).

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.

Born on July 5, 1919 in Romania, Franz studied the adrenal as a physician scientist in post-World War II Innsbruck, Austria. He continued this work at Harvard Medical School, where he held a World Health Organization fellowship in clinical endocrinology in 1948. In 1949, he moved to the University of Minnesota, which saw his breakthrough experiments (Figure 2) 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 (Halberg, 1953; Halberg *et al.* 1953). Franz coined the term circadian, after documenting that biologic rhythms tip the scale between health and disease and even between life and death (Halberg, 1959). 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 (Barnum *et al.* 1958). He subsequently added pineal feedsideways and the understanding that there are endogenous physiologic networks that respond to the cosmos (Halberg *et al.* 1986, 2012b).

Beyond circadians, Franz demonstrated that many other built-in cycles resonate in part with their counterparts in our broad environment. His recent work



Fig. 2. Franz Halberg counting eosinophils in 1949 at the University of Minnesota.

focused on building a growing edifice of shared periodicities with bridges across disciplines (Halberg *et al.* 2008, 2013). 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 chronosphere (Halberg *et al.* 2012a). 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 (Halberg *et al.* 2003c). Franz showed that a calorie is different whether it is consumed at breakfast or dinner (Halberg *et al.* 1953, 1995). 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 (Halberg *et al.* 2013), appropriate circadian timed treatment more than halved the risk of stroke and other adverse cardiovascular events.

In 1999, the editor of NEL wrote a special laudatio to honor Franz on the occasion of his 80th birthday. In it, Peter G Fedor-Freybergh (1999) recognized common interests between issues covered in his journal and Franz's multidisciplinary approach and focus on prehabilitation (to reduce the need for rehabilitation). He ends his "hommage" by citing truth and creativity as common denominators of Franz's life, which gave him "a great confidence for the coming (21th) millennium". Ten years later, he published another birthday celebration of Franz authored by Miroslav Mikulecky (2009). In November 2002, Franz, Othild and I had the very great pleasure to meet in person Peter G Fedor-Freybergh and NEL's Art Director, Lili Maas. It was on the occasion of a meeting on "Time structures – chronomes – in child development" organized in Munich, Germany, by Prof. Dr. Dr.h.c. Theodor Hellbrügge. There, colleagues from around the world gathered to discuss the developing time structures and how they organize in early extrauterine life. At the meeting, Franz was awarded the prestigious Arnold Lucius Gesell Prize. The Proceedings of the meeting were published in NEL (Cornelissen *et al.* 2003).

Each year, Franz liked to summarize the year's findings as a way to thank his co-workers and to send for Christmas the Center's Season's Appreciations (Halberg *et al.* 1999a, 2000a, 2001a, 2002, 2003b). As Franz liked



Fig. 3. Franz Halberg (right) with Earl E Bakken (middle) and Germaine Cornelissen (left). Picture taken in August 2012.

to coin new words, semantics needed to be defined (Halberg *et al.* 1999c,d). Whether his research dealt with melatonin (Halberg *et al.* 1999b; Maggioni *et al.* 1999; Tarquini *et al.* 1999; Salti *et al.* 2006) or blood pressure (Halberg *et al.* 2000b; Watanabe *et al.* 2003), Franz always paid special attention to the development of new methodological approaches to further resolve time structures in biology and their associations with the environment (Halberg *et al.* 2003a). Franz was equally keen in using state-of-the art technology for the noninvasive monitoring of vital signs, as a means to enter the impenetrable “normal range” of physiological variation. To describe initiators of modern mapping of our make-up in time, Franz paid tribute in print to Earl E Bakken (Figure 3), who also served as a local time-witness of concerns about chronomics in Minnesota (Halberg *et al.* 2001b).

Franz’s lifetime accomplishments are summarized in his over 3,500 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 (Kiser, 2005), and colleagues in Russia and Azerbaijan honored him as Lord of Time (2011).

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 honorary member of the Romanian Academies of Science and Medical Sciences. He was also elected Corresponding Member of the French National Academy of Medicine. Franz 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). 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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