On Sunday morning June 9, 2013, a legend and one of the greatest scientists of the 20th and 21st centuries left us. His close associates also lost a very dear friend and a mentor who never ceased to inspire. Franz Halberg’s passing at 93.93 years of age (Franz always listed his age most accurately!) leaves a void that cannot be filled.

Franz Halberg (Fig. 1) will be remembered for founding the fields of chronobiology (1, 2), chronomics (3-5) and chronobioethics (6, 7). 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. An essential element was the key principle Franz followed throughout his life’s work, namely to “measure in time what is measurable and render measurable what as yet is not” (Omnia metire quaecumque licet et immensa ad mensuram tempestive redige). 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 (8-18).

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.

Born on July 5, 1919 in Romania, Franz studied the adrenals 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 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 (19, 20). Franz coined the term circadian, after documenting that biologic rhythms tip the scale between health and disease and even between life and death (21, cf. 22, 23). His results were widely published, including a 1969 citation classic (1). 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 (24). He subsequently added pineal feedsideways and the understanding that there are endogenous physiologic networks that respond to the cosmos (25, 26).

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 (27-29), addressing wide-ranging applications from the optimization of individualized health care to concerns for the health of societies. He 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 chronospheric (30). 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 showing that timing cancer treatment according to marker rhythms improves outcomes both in terms of heightened efficacy and lesser undesired side effects (31-34), for showing that a calorie is different whether it is consumed at breakfast or dinner (20, 35-37), and for his work in preventive cardiology by scree ning for abnormal patterns of blood pressure variability (38-41). Corresponding circadian timed treatment more than halved the risk of stroke and other adverse cardiovascular events. “Primum nil nocere” (above all, do no harm) prompted Franz to advocate the individualization of treatment, guided by marker rhythms (32, 42).

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 (43), and colleagues in Russia and Azerbaijan honored him as Lord of Time (44).

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 93.93 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 the last recipient of a lifetime career award from the National Institutes of Health.

Whether at the lab (Fig. 2) or at international meetings (Fig. 3), it has been a real privilege to closely work (or rather, in Franz’s words, “have fun”) alongside such a prominent scholar at the frontiers of science. Franz’s insistence on quantification by means of inferential statistics made possible the exploration of lawful variations taking place within the physiological range. Particularly in relation to blood pressure and the hormones implicated in its variability, Franz clearly documented the merit, or rather the critical need to assess
rhythmicity as an indispensable control (45). He showed that the circadian rhythm in blood pressure could desynchronize from 24 hours when other vital signs monitored concomitantly remained 24-hour synchronized (46), debunking the then assumption that changes in blood pressure were primarily the result of changes in activity. He mapped multi-frequency rhythms of the cardiovascular system from birth (47) to old age (48). In early extraterine life, he found that circadian rhythms in blood pressure and heart rate were expressed but that they were in antiphase with the maternal rhythms (49, 50). He showed the prominence of about-weekly changes in newborns, synchronized by the time of birth rather than by the social schedule, adding critical evidence for the partly endogenous nature of circaseptan rhythms (51, 52). Franz went on to derive reference values for the circadian variation in blood pressure and heart rate, separately by gender in different age groups (53, 54). On their basis, he defined Vascular Variability Anomalies (VVAs) and Disorders (VVDs) that in several outcome studies were associated with a large increase in cardiovascular disease risk, beyond the risk related to an elevated blood pressure itself (38, 55). It was Franz Halberg’s recognition that variability and not homeostasis is the essence of life that put chronobiology on the map (1, 19, 21). The discovery of important physiological problems and their mechanisms is certainly one of Franz’s major achievements. But the science of chronobiology would not have developed without his changing the very fundamentals of medicine and biology still prevailing today. The impact he 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.

References


