Father Time

By Kim Kiser

The University of Minnesota's Franz Halberg, M.D., is known around the world for his study of the relationship between the body's time structure and health. Will his ideas find their way into mainstream medicine in this country?

There is no sign indicating you've arrived at the Halberg Chronobiology Center, no clues as to the type of work taking place here or the accomplishments that have come out of this warren of tiny vanilla-walled offices on the seventh floor of the University of Minnesota's Mayo Building. The center is practically invisible on campus, and that lack of visibility disappoints Franz Halberg, M.D., the man for whom it is named and who invented the concept of chronobiology, the study of the body's time structure and its effect on health. But in the eyes of chronobiology researchers around the world, the center's stature is huge.

Halberg occupies Room 715, a time capsule of his 50-plus-year career at the university that's crammed with bookshelves stacked with copies of journals and papers he's edited or written over the years. The 86-year-old Halberg can be found there just about any time any day of the week when he's not traveling to places such as Mumbai, New Delhi, or Moscow to present invited lectures or receive awards. On an early September Thursday, Halberg, who invented the term "circadian rhythm" (from *circa*, which means "about" and *dies*, which means "day"), is poring over a desk scattered with the rough drafts of 15 abstracts he'll present at a conference the following week.

Halberg, who was born and educated in Romania, is the epitome of an old-school European gentleman. A tall, bespectacled man who apologizes for being a bit hard of hearing, he welcomes guests to his office as if he's welcoming them into his home, offering copies of papers and publications as if they were home-baked cookies. Once the formalities are over, he gets down to business.

He explains how we don't just have circadian rhythms of approximately 24 hours, but circaseptan or weekly rhythms, trans-year rhythms that might last 1.3 years, not to mention that aspects of our health might follow the cycles of sun spots and other rhythms whose signatures in physiology he and his colleagues are just discovering after decades of research. As he talks, it becomes clear that Halberg is a man with a mission: to make physicians aware that understanding the body's rhythms and patterns—and recognizing changes in them—can be important to preventing and treating disease. "One of the big mistakes that's made is to believe that we can treat by clock hours," he says. "We have to treat by body times."

■ The Rhythms of Life

Halberg first became interested in the principles behind chronobiology as a high school student, accompanying physician friends of his parents in their practice. In those days before the discovery of sulfonamides and penicillin, he noticed that patients with pneumonia either recovered or died in seven days. After medical school during the height of World War II, Halberg worked in a French-occupation Army hospital, where he diagnosed gonorrhea in two soldiers who had been with the same prostitute on consecutive days. The soldier who was exposed later was the first to show a negative smear, suggesting to Halberg that the time between infection and the start of treatment could be important.

Halberg came to the United States in 1948 to do an endocrinology fellowship at Harvard Medical School. His acquaintance with Maurice Visscher, M.D., the internationally known head of the University of Minnesota Department of Physiology, led him west the following year. Halberg picked up on an observation he had made while studying corticoids. He counted eosinophils, circulating white blood cells, in mice and found that the counts rise and fall during a 24-hour period.

In his Minnesota lab, Halberg studied the eosinophil counts of different inbred mouse strains. As he describes that early research, he pulls a black book of his early papers off a shelf and turns to the exact yellowed page of a

Franz Halberg, M.D., has fought long and hard to make chronobiology part of medical practice.

Photo by Steve Wewerka

At a Glance

■ Franz Halberg, M.D.

Professor of laboratory medicine and pathology, physiology, biomedical engineering, and oral medicine; co-director, Halberg Chronobiology Center, University of Minnesota

Education: M.D., University of Cluj, Romania, 1943; Fellowship in Medicine, Harvard Medical School, 1948-49

Family: Married to Othild Schwartzkopff, M.D., clinical assistant professor of pediatrics emerita; daughters Francine, a radiation oncologist and clinical associate professor at the University of California, San Francisco, and Julia, director of health services at General Mills and an adjunct professor of occupational and environmental health at the University of Minnesota

Number of publications: 3,005 as of October 2005

Languages fluent in: English, German, French. "He's one of those people who's gifted in languages," says daughter Julia, who adds that he also dabbles in Italian and a few other languages.

Interests: Tennis (he was once the faculty tennis champion at the university); writing poetry ("when I want to let some steam off, I do it"), and, of course, his work. "He loves what he does. It's not a job, it's truly his life. Retirement for him is a bad word," says Julia.

study showing that certain strains of black mice, for example, had a high count of around 1,000 at noon and a low of approximately 300 at night but that certain white mice had high counts of only 200 at noon and lows of 20 at night. "Each strain had a different extent of change," he says, thus showing that genetics plays a role in determining circadian rhythm.

In 1950, Halberg and his team also analyzed eosinophil counts and temperature variations in sighted mice and in mice that had been blinded in order to remove environmental cues such as day and night that help keep the body's time structures in sync. They identified rhythms in the sighted mice that rose and fell at approximately the same time each day. In the blinded mice, those rhythms shifted and peaked earlier each day. In addition, they found that some individuals from the same strain of blinded mice had a 23.5-hour cycle, while others had a 23.4-hour cycle, but none had an exact 24-hour cycle, again showing the influence of genetics. In exploring the implications of those cycles, Halberg found that one group of mice developed seizures when exposed to extremely loud noise at 10 p.m., the active part of their day. A different group that was exposed to the noise at noon—during their rest cycle—did not. He also discovered that mice that were given a potential poison or high doses of a drug at one time of the day died, while a group given that same compound 12 hours earlier or later lived.

Halberg eventually became the first researcher to successfully apply the idea of working with the body's rhythms to treat cancer in people. With his oldest daughter,

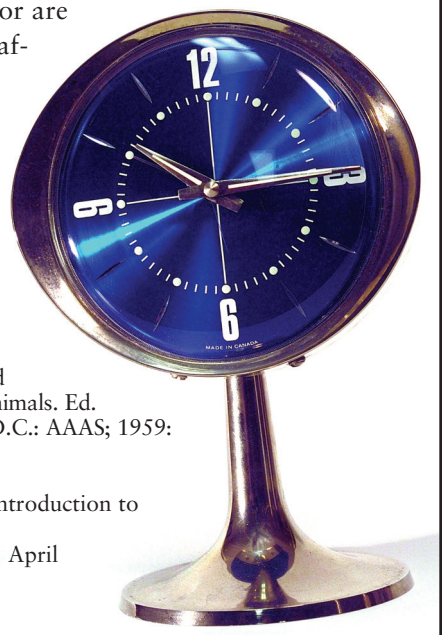
What Makes Our Clocks Tick

Within a sliver of brain tissue the size of a pin's head lie the springs and gears of our biological timekeeping. Made up of a tiny bundle of nerve cells within the brain's hypothalamus, this mechanism, called the suprachiasmatic nucleus (SCN), keeps track of the time of day, and coordinates our sleep patterns and daily fluctuations in heart rate, blood pressure, temperature, and secretion of some hormones.

The SCN uses information from light receptors in the retina and then sends signals along its own pathway of nerves to the hypothalamus and the pineal gland to release hormones that coordinate body functions.

When external cues such as light, darkness, or the sound of an alarm are removed, the SCN becomes confused. The body still maintains its rhythms but not in an organized 24-hour synchronized cycle. Body temperature will still follow a nearly 25-hour cycle, but the rhythms of sleep and other daily activities could change.

In animals in which the SCN has been destroyed, the circadian rhythm of some variables such as temperature is altered. The circadian rhythm is not obliterated, however, nor are all variables equally affected. –K.K.



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Francine, now a radiation oncologist in the San Francisco area, Halberg traveled to Chandigarh, India, in the late 1960s to work with a local physician who was doing radiation therapy on patients with large oral tumors. Halberg and his colleagues used tumor temperature, a probable reflection of metabolic activity, as a marker to time treatments. Patients were divided into groups that received treatment eight hours before peak temperature, four hours prior to peak, at peak, four or eight hours after peak, and at the convenience of the patient or clinic. More than 60 percent of patients who received treatment when the tumor was at peak temperature were alive and disease-free two years later. "Treating them at peak tumor temperature doubled the two-year disease-free survival," he says, adding that, based on new data, it appears to be possible to use core body temperature when monitoring tumor temperature isn't practical. (The first patient to receive chronotherapy according to the rhythm of her core temperature was alive decades later, Halberg notes.)

When Halberg's first wife, Erna, whom his youngest daughter Julia describes as "his right-hand person" in the lab, fell ill with late-diagnosed, advanced ovarian cancer in the early 1990s, his team quantified rhythms in markers in her saliva, urine, blood, body temperature, and blood pressure that would help optimize the timing of her treatment. "We were able to work with her doctors, and even though we didn't change the dose of chemotherapy, we were able to change the timing of it," says Julia, who now directs health services at General Mills in Golden Valley. "She did live beyond what was initially predicted. And the timing of her treatment was a factor."

■ Hidden Dangers

Halberg's work has been very much a family affair, with his wife and daughters working alongside him in the lab and participating in numerous human studies. What's perhaps been his most ambitious venture began with Halberg, Erna, and their then preteenaged daughters monitoring their blood pressure several times a day to look for patterns and variations. Halberg gained new insight into a potential cause of stroke after Julia and her mother did 24-hour round-the-clock blood pressure monitoring on rats that were bred to develop high blood pressure and identified circadian hyperamplitude tension, now called "CHAT," an increased swing in the amplitude of blood pressure that develops before a rise in mean blood pressure readings.

The results of that study eventually led to the creation of the Womb to Tomb project some 15 years ago, which involved monitoring the blood pressure of pregnant women and neonates. The initiative has since been renamed the BIOCOS (short for biosphere and cosmos) project and broadened in its scope. (The purpose, says Germaine Cornelissen-Guillaume, Ph.D., co-director of the Halberg center, "is to monitor heart rate and blood pressure and other variables for preventive reasons in maintaining good health and also to understand better the effects of the cosmos on our physiology and pathology.") As part of that project, the Halberg Center has collected blood pressure measurements from more than 2,800 individuals in 23 countries who have monitored their pressure every 30 minutes for at least seven consecutive days. Halberg and his team use the data to determine normal patterns and identify those that may indicate risk for disease and to compare variations among subjects of the same age and gender. Halberg has been monitoring his own blood pressure and heart rate continuously for 16 years, the sound of the blood pressure cuff inflating and deflating every half hour serving as a constant reminder.

In 1987, colleagues in Tokyo began a six-year prospective study of nearly 300 patients and found that CHAT was a greater risk factor for ischemic stroke than obesity, high cholesterol, family history, being male, consuming alcohol, smoking, and having an elevated mean blood pressure. In addition, investigators found that patients with diastolic CHAT (those whose diastolic pressure varies by 20 mm/Hg or more during the day) have a risk for ischemic stroke within six years that is 8.2 times greater than those whose circadian blood pressure amplitude is within a normal range.

Using data from the BIOCOS project, Halberg and colleagues have found other patterns that could place patients at greater risk for cardiovascular events, such as excessive pulse pressure (the difference between systolic and diastolic pressure when the heart contracts and relaxes), reduced 24- or 168-hour heart rate variability, and oddly timed peaks and valleys in blood pressure but not in heart rate. They also discovered that taking blood pressure medication at an undesirable time can cause CHAT, making the timing of treatment important.

If there's one message Halberg would like to impart to the medical community, it's that evaluating a patient's blood pressure using one reading taken during an office visit is like trying to understand the plot of a film by looking at a single frame. The story told by that image may cause physicians to treat people who may not need it or to miss cases that need treatment. For that reason, he would like to see all patients monitored for at least seven consecutive days. "Certainly, if you can pick up a risk greater than hypertension for stroke, myocardial infarction, kidney disease, and blindness, why not? It's much cheaper to pick it up early. That's the immediate pay dirt not only for care providers but for the person on the street," he explains.

■ Ahead of His Time

Halberg's research on the body's rhythms documented that cycles characterizing the solar wind, sun spots, and geomagnetic storms could have a more important effect on our bodies than the alternation of the seasons. For example,

fatal heart attacks follow about a 10.5-year cycle in Minnesota in keeping with the solar activity. Such findings have elevated him to celebrity status at chronobiology conferences. "He is worshiped around the world as one of the great leaders and elucidators of what's happening in living things, particularly in the human body," says Earl Bakken, co-founder of Medtronic Inc., who has known Halberg since the early 1950s, when he developed devices for use in animal studies. Bakken has traveled with Halberg to China and Norway. "It's really interesting to see how scholars in foreign countries hang on to him and want to get a word from him and are entranced by what he has to say. When he's overseas, which he is a lot, people listen to him intently. … In many countries, they think he is tremendous." In fact, a group of physicians in Moradabad, India, even named an 18-bed hospital after him in 2004. And entire cities in Japan have taken part in the blood pressure monitoring project. "They're wonderful people," Bakken says of Halberg and his staff, "and can contribute so much to humanity, if humanity would listen to them better."

Halberg admits it has been a struggle to convince physicians, scientists, and others in the United States of the importance of chronobiology (in an interview published in the *Journal of Circadian Rhythms* in 2003, Halberg said his department head considered some of his early studies "foolish," and efforts to get the city of Roseville, where Halberg lives, to do seven-day blood pressure monitoring in the late 1990s were shelved). "It's been a bloody fight to put across what is today generally accepted as circadian rhythms, that you have built into you a time structure as a genetic feature with ups and downs that determines how you respond to a drug, or a physical stimulus, or to emotions."

One reason why chronobiology has not become part of mainstream medicine is because it's not a consistent component of medical education. A 1996 Gallup study conducted for the American Medical Association found that more than half of 320 physicians surveyed were not familiar with chronobiology and that only one-third had been taught chronobiology in medical school.

"The other thing is that there has not been the type of randomized controlled study that changes practice," says Dana Johnson, M.D., a professor of pediatrics and director of the division of neonatology at the University of Minnesota, who worked with Halberg to discover that very premature babies have a predominant seven-day rhythm in blood pressure and heart rate that matures into a 24-hour rhythm as they get older. Many of Halberg's papers have been published in journals that don't cross the desk of the average physician in the United States. And the articles that have been published here aren't always easy to comprehend. "He developed so much of the language of chronobiology, which is OK, but it's hard for someone else who isn't acquainted with that language," Bakken says.

Practical considerations also come into play when trying to convince physicians to do things like continuous seven-day blood pressure monitoring. "It's not easy for a doctor to have a patient come in and say 'I want your blood pressure every half hour for two weeks.' Patients are reluctant to submit to that," Bakken says. (Halberg and his team are working with a group of engineers to design a blood pressure monitor that is inexpensive and unobtrusive.)

Johnson believes Halberg's ideas about blood pressure deserve attention. "This is a huge public health issue associated with the major causes of morbidity and mortality in Western life. I think he feels frustrated that more people haven't embraced this type of predictor," says Johnson, who recently recorded his own blood pressure for seven days and found that it was above the normal limits for rhythm parameters and sought treatment.

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Many of those who've worked with Halberg, including his daughter Julia, who does blood pressure monitoring on some of the patients who come to her clinic, believe chronobiology is just in its infancy and that Halberg is indeed a man who's ahead of his time. "Franz has made contributions that will be remembered long into the future," says Johnson, who adds we're just starting to peek through the window into such phenomena as how sun-spot cycles may affect growth. Bakken has noticed researchers starting to do studies similar to those Halberg did 50 years ago. "He's one of the really great scientists we have here, and we need to recognize that more," Bakken says, "But he's impatient. He wants it all happening before he goes."

In the meantime, Halberg will continue to try to make it happen, working to his own seven-day-a-week cycle, discovering new rhythms in the body and nature, studying connections between the weather in space and events in the human body, and trying to convince the medical community to think beyond what is considered a "normal" blood pressure reading. "There have been many fights in medicine, and this is still a fight," he says with the tenacity of one who's determined to win. **MM**

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