

Reflecting on activities at the Halberg Chronobiology Center during this pandemic year of 2020, we can be grateful for so many things, large and small. First and foremost, it has been a great pleasure to continue cooperation with all our colleagues here and abroad. This year's highlights are summarized below.

Last year's commemorations of the 100<sup>th</sup> anniversary of the birth of Franz Halberg continued well into 2020. On February 27, 2020, Michael Blank, Professor at the Russian Research Center for Radiology and Surgical Technologies, organized in St. Petersburg a Scientific Conference "Chronobiological Aspects in Main Diseases Diagnosing and Treatment", which was dedicated to Franz's memory. He invited Germaine to deliver the opening lecture, a wonderful opportunity to reminisce on the strong and long-lasting cooperation between colleagues in Russia, Franz and the HCC. Friendship's University of Russia in Moscow also organized an International Conference on "Chronobiology in Medicine and Sport", which was dedicated to the 100<sup>th</sup> anniversary of the birth of Franz Halberg, held virtually on December 7-9, 2020, for which Germaine served as Vice President. The World Heart Journal plans on a supplemental issue to publish the long abstracts of the many presentations delivered at the meeting, including those from the HCC.

Despite the pandemic and our working remotely from home since mid-March, the HCC remained active and productive, enjoying the continued cooperation of colleagues and friends locally, nationally, and internationally. The focus of the Center remains centered on the monitoring of blood pressure in health and disease and on changes in the time structure of heart rate variability and activity in astronauts during long missions on the International Space Station (ISS).

As part of our project with Kuniaki Otsuka, Professor at Tokyo Totsuka Royal Clinic, Women's Medical University's Executive Medical Center, Japan, and in cooperation with members of the Japanese Space Agency, we extended the ECG monitoring of astronauts from 24-hour to 48-hour records, and we added 2- to 4-day actigraphy. The data show that the circadian rhythm of heart rate strengthened in space and that sleep quality improved. These effects may be mediated by magnetic fluctuations, which were associated with enhanced parasympathetic tone at night and the activation of the brain default model network (DMN). Activation of the adaptive process by the DMN may involve increased infraslow oscillations (with a period of about 1 minute) of heart rate variability, starting at night. Several papers summarizing our results have been submitted for publication.

Our project on the BIOSphere and the COSmos (BIOCOS) continues on several fronts, from 7-day/24-hour ambulatory monitoring, thanks to support from the A&D Company (Tokyo, Japan), to the testing of wrist-worn blood pressure monitors in cooperation with El Nolley, Chris Adams, and Larry A Beaty, volunteering IEEE engineers of the Phoenix Project. Despite efforts by several companies to develop cuff-less blood pressure devices based on photo-plethysmography, wrist-worn blood pressure monitors using an inflatable cuff remain more accurate and more reliable, but remain limited to manual use. In view of the importance of obtaining undisturbed measurements during sleep for a reliable assessment of the circadian variation in blood pressure, modifications of cuff-based wrist monitors need to be designed to render them truly ambulatory.

The analysis of new and existing ABPM databases is also within the scope of BIOCOS' mandate. In addition to our further demonstration that ABPM needs to be performed over spans longer than 24 hours and that data have to be interpreted in the light of reference limits that account for the

circadian variation, gender differences, and changes as a function of age, we showed how such simple considerations are ignored in current clinical practice. The lower blood pressure values in women as compared to men observed in normotension are no longer seen in populations treated with anti-hypertensive medications, indicating that all adults 18 years and older receive treatment aimed at reaching the same blood pressure targets, irrespective of gender or age. Analysis of ABPM data collected as part of the DASH (Dietary Approaches to Stop Hypertension) study with a former undergraduate student, Fatimatou Saka, also showed circadian stage-dependent effects that are gender specific. These results have been published in the *Journal of Human Hypertension*.

As a complementary approach to ABPM, with Software Engineer Larry A. Beaty, we continued work to analyze beat-to-beat blood pressure waveforms recorded over minutes or at most a few hours in a project by David Jacobs, Professor of Epidemiology, and Daniel Duprez, Professor of Cardiology, both at the University of Minnesota. David and Daniel showed that the characterization of features of the blood pressure waveform is also predictive of cardiovascular disease risk. We streamlined existing R code to analyze the data automatically, and we are currently working on improving the identification of markings corresponding to specific events that occur within a cardiac cycle.

Work on open-angle glaucoma continued with Denis Gubin, Professor at Tyumen State Medical University, Russia. Results on the circadian rhythm of intraocular pressure, which has an inverted phase in patients with an advanced condition but not in patients with a stable condition, are being published in the *International Journal of Molecular Sciences*. The effect of long-term administration of melatonin is currently being investigated in these patients, including any benefits to be derived from a personalized strategy of melatonin administration.

In January, following tradition, Yoshihiko Watanabe, emeritus Professor of Internal Medicine at Tokyo Women's Medical University, Japan, spent a week with us at the HCC. Analysis of additional 7-day/24-hour ABPM records from his patients further documented the merits of a personalized approach to the optimization of anti-hypertensive treatment by timing. When considering all abnormal patterns of variability in blood pressure and heart rate, beyond the mere elevation in the 24-hour mean blood pressure, which are all associated with increased cardiovascular disease risk, more than 50% of patients are likely to benefit from personalized chronotherapy. Even if on the average, outcomes may be improved by treating everybody indiscriminately in the evening, such a strategy harms those patients with distinct abnormalities of their blood pressure variability. Yoshihiko's planned visit in September had to be cancelled due to the pandemic, as had the visit of Kuniaki in May and that of Walter Kofler, President of the International Academy of Science – Health and Ecology, in November, all due to the pandemic.

In response to an invitation from Nandu Goswami, Acting Head of the Physiology Division at the Medical University of Graz, Austria, the HCC participated in an interdisciplinary, international application to Horizon 2020, the EU funding program for research and innovation. Our proposal, "CommuniCare" aimed at mitigating the risk of falls in the elderly and assessing the impact on active and healthy aging and on the cost of long-term care. While our proposal was not funded, a review of the roles of circadian rhythms and melatonin as critical factors underlying falls, and aging more generally, was published in *Clinical Interventions in Aging*.

Plans with our colleagues Mei and Paul Bigliardi, Professors in the Department of Dermatology at the University of Minnesota, to explore effects of microgravity and magnetic disturbances on skin

growth in space, are currently on hold. Their interest in chronobiology extended to other applications, and a protocol has been designed to optimize the timing of treatment of chronic pruritus in atopic dermatitis with the opioid antagonist naltrexone.

At the HCC, we are now all working remotely, which necessitated some changes. Cathy Lee Gierke, who had taken a leave of absence to travel to Greece, had to return to Minnesota early. Upon her return, she decided to step down from her position at the HCC. She is still volunteering her time to help colleagues and students use her CATkit program. Mary Sampson was setup with a new laptop, so that she could continue her work editing manuscripts, notably for the World Heart Journal. She also started a new project of assembling key words to be added to the bibliography of Franz Halberg, when his over 3,600 published titles will all be made fully searchable in scanned .pdf files. This endeavor will also serve in part for our “atlas of chronomes” (chronomes are broad time structures consisting of multi-frequency rhythms, trends with development, age, and disease progression, and elements of chaos). The atlas of chronomes is to be a repository of multi-frequency rhythm characteristics of major physiological functions in health and disease. Linda Sackett-Lundeen has now taken over the assembling and scanning of the papers published by Franz Halberg. Most publications up to 1996 are now ready to be uploaded in our forthcoming fully searchable electronic database. Linda is also involved in a number of other projects, from literature reviews to data analyses. This year, she completed the digitalization of the 43-year record of self-measurements of the late Erhard Haus, Professor of Laboratory Medicine and Pathology at the University of Minnesota, and former Head of Pathology at Regions Hospital, Saint Paul, Minnesota. Her results from analyses of the circannual variation in his vital signs were presented at the Annual Workshop on Noninvasive Methods in Cardiology, organized by Jarmila Siegelova, Professor at Masaryk University, Brno, Czech Republic. Our weekly lab meetings are now done by Zoom. As part of our discussions of ongoing projects, we continue to benefit from the expertise of and advice from Larry A. Beaty and from A. Chase Turner. Topics of interest remain the automatic non-invasive, cuff-less monitoring of blood pressure, and the use of Mathematica to illustrate cosinor-related methods for the analysis of periodicities.

Several students came to the HCC to work on small research projects. Their topics varied from the analysis of locomotor activity data collected from a wrist-worn device from Ambulatory Monitoring, Inc. to the analysis of cortisol and blood pressure in newborns, infants, and children to map the development of circadian rhythms in these variables. Several students also came to the HCC to write their capstone. One topic related to the role of circadian rhythms related to sleep and academic performance reported on the importance of regularity in the sleep-wake schedule. Another discussed the negative effect of sleep deficiency on the progression of Alzheimer’s disease. A third reviewed the effect of meal timing and frequency of meals on lipogenesis and weight, confirming the benefit of consuming more calories earlier in the day. Work with a former undergraduate student on the relationship between blood pressure and activity was extended to illustrate how methods of time series analysis can be performed and automated in Excel. This work was presented at Brno’s Annual Workshop on Noninvasive Methods in Cardiology.

Work at the HCC attracted several invitations to lecture and other distinctions. As a follow-up of her participation at the 5<sup>th</sup> International Conference for Advanced Cardiac and Heart Transplant (King of Organs 2019), Germaine was invited to publish her work related to environmental effects on human health in a special issue of International Journal of Environmental Research and Public Health by Professor Rollin McCraty, Director of Research at the HeartMath Research Center. Elizabeth Luszczek’s results with us on circadian rhythms of vital signs and metabolomics in patients

admitted to the Intensive Care Unit, now published in *Frontiers in Neurology*, were featured on the website of the Minnesota Supercomputing Institute. Jarmila's annual workshop in Brno was held this year on October 15. The HCC also participated at two other meetings in Tyumen, Siberia, by invitation from Denis Gubin. On August 27, Germaine gave a lecture on "Healthcare systems at a crossroad: critical importance of embedding chronobiologic principles now" at the Arctic Conference organized by Tyumen's Regional Scientific and Educational Centre. As part of Tyumen's Medical University Annual Therapeutic Forum, an international online conference on "Chronodiagnostic and chronotherapy: The Fundamentals of Digital Health" was held in November, where Germaine gave a lecture on "Chronotheranostics: guiding chronotherapy in light of the chronodiagnosis - a step toward personalized medicine".

This year, with great sadness, we mourn the loss of a dear friend and colleague, Pietro Cugini. He was a great and distinguished physician-scientist. Chronobiology, the field he helped shape and guide, will miss him dearly. His obituary, published in *Chronobiology International*, summarizes the many contributions Pietro made throughout his rich career studying the renin-angiotensin-aldosterone system.

The HCC continues to benefit from cooperation with many more colleagues locally, nationally, and internationally. In particular, we are grateful to Drs. Francine and Julia Halberg who serve as advisors to the HCC. Their continued support of activities at the HCC is much appreciated.

Germaine Cornelissen  
Professor, Integrative Biology and Physiology  
Director, Halberg Chronobiology Center  
Coordinator, Project on the BIOSphere and the COSmos (BIOCOS)  
[corne001@umn.edu](mailto:corne001@umn.edu)  
<http://halbergchronobiologycenter.umn.edu>

1. **Cornelissen G**, Otsuka K, Gubin D. Honoring Gennady Gubin and his lifetime achievements. *Journal of Chronomedicine* (“Tyumen Medical Journal”) 2019; 21(1): 8-13; (In Russian). doi: 10.36361/2307-4698-2019-21-1-8-13
2. Gubin DG, **Cornelissen G**. Factors that must be considered while solving the problem of adequate control of blood pressure. *Journal of Chronomedicine* (“Tyumen Medical Journal”) 2019; 21(1):14-20; (In Russ). doi: 10.36361/2307-4698-2019-21-1-14-20
3. Gubin D, Weinert D, **Cornelissen Guillaume G**. Chronotheranostics and chronotherapy – frontiers for personalized medicine. *Journal of Chronomedicine* (“Tyumen Medical Journal”) 2020; 22 (1): 3-23; doi:10.36361/2307-4698-2020-22-1-3-23
4. **Cornelissen Guillaume GG**. Aktivitätsbericht des Halberg Chronobiology Center (HCC) 2019. <https://leibnizsozietaet.de/aktivitaetsbericht-des-halberg-chronobiology-center-hcc-2019-uebermittelt-von-unserem-mitglied-germain-g-cornelissen-guillaume/> (29 Januar 2020).
5. Singh RB, **Cornelissen G**, Mojto V, Fatima G, Wichansawakun S, Singh M, Kartikey K, Sharma JP, Torshin VI, Chibisov S, Kharlitskaya E, Al-baraweed OA. Effects of circadian restricted feeding on parameters of metabolic syndrome among healthy subjects. *Chronobiology Int.* 2020; 37 (3): 395-402.
6. Singh RB, Fedacko J, Elkilany G, Hristova K, Palmiero P, Pella D, **Cornelissen G**, Isaza A, Pella D. 2020 Guidelines on pre-heart failure in the light of 2D and 3D speckle tracking echocardiography. A scientific statement of the International College of Cardiology. *World Heart Journal* 2020; 12 (1): 51-70.
7. **Cornelissen Guillaume G**, Gubin D, Beaty LA, Otsuka K. Some near- and far-environmental effects on human health and disease with a focus on the cardiovascular system. *International Journal of Environmental Research and Public Health* 2020. doi:10.3390/ijerph17093083 (by invitation).
8. **Cornelissen Guillaume G**, Gubin D, Otsuka K. Effects of space weather on human physiopathology. <https://encyclopedia.pub/1375>
9. **Cornelissen G**, Sothern RB, Sackett-Lundeen L, Uezono K, Otsuka K. Obituary: Pietro Cugini (13 December 1936 – 6 April 2020). *Chronobiology International*. DOI: 10.1080/07420528.2020.1781361
10. Saka F, **Cornelissen G**. Chronobiologic assessment of the effect of the DASH diet on blood pressure. *Journal of Human Hypertension*. DOI : 10.1038/s41371-020-00408-0
11. Otsuka K, **Cornelissen G**, Kubo Y, Kikuchi T, Yamanaka G, Murakami S. Preventing progression to senile dementia in community-dwelling citizens of a small Japanese village. *American J of Biomedical Science & Research*. DOI: 10.34297/AJBSR.2020.10.001462
12. Luszczek ER, Parsons LS, Elder J, Harvey SB, Skube M, Muratore S, Beilman G, **Cornelissen-Guillaume G**. Metabolomics pilot study identifies desynchronization of 24-hour rhythms and distinct intra-patient variability patterns in critical illness: A preliminary report. *Front. Neurol. - Sleep Disorders*. DOI: 10.3389/fneur.2020.533915)
13. Goswami N, Abulafia C, Vigo D, Moser M, **Cornelissen G**, Cardinali D. Falls risk, circadian rhythms and melatonin: current perspectives. *Clinical Interventions in Aging* 2020; 15: 2165–2174.
14. **Cornelissen-Guillaume G**. The First Cell and the Human Costs of Pursuing Cancer to the Last. Azra Raza. Basic Books, 2019. 368 pages. Book Review. *The Key Reporter* (Phi Beta Kappa Soc.) 2020 August.
15. Neroev V, Malishevskaya T, Weinert D, Astakhov YS, Astakhov SY, Kolomeichuk S, **Cornelissen G**, Kabitskaya Y, Boiko E, Nemtsova I, Bogdanova D, Gubin D. Disruption of 24-hour rhythm in intraocular pressure correlates with retinal ganglion cell loss in glaucoma.

International Journal of Molecular Sciences Int. J. Mol. Sci. 2021, 22, 359.  
<https://doi.org/10.3390/ijms22010359>.

16. **Cornelissen G**, Farah Z, Gubin D, Gumarova L, Sackett Lundeen L, Kazlausky T, Otsuka K, Siegelova J, Beaty LA. Chronobiologic analyses of weeklong around-the-clock records of simultaneously monitored blood pressure and activity. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2020*. Masaryk University, Brno, Czech Republic 2020; 19-25.
17. Sackett Lundeen L, Beaty LA, Siegelova J, Watanabe Y, **Cornelissen G**. Some lessons learned from a 43-year record of self-measurements by a physician-scientist. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2020*. Masaryk University, Brno, Czech Republic 2020; 27-41.
18. Goswami N, Abulafia C, Vigo DE, Moser M, **Cornelissen G**, Cardinali D. Falls and falls-related injuries: do circadian rhythms and melatonin play important roles? In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2020*. Masaryk University, Brno, Czech Republic 2020; 47.
19. Siegelova J, Dunklerova L, Dobsak P, Havelkova A, Vanat M, Singh RB, **Cornelissen G**. Best time of exercise according to circadian rhythm. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2020*. Masaryk University, Brno, Czech Republic 2020; 49-74.
20. Siegelova J, Dunklerova L, Havelkova A, Dusek J, Pohanka M, Dobsak P, **Cornelissen G**. Night-to-day blood pressure ratio during seven-day ambulatory blood pressure monitoring. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2020*. Masaryk University, Brno, Czech Republic 2020; 93-106.
21. Gubin D, Petrov IM, Khasanova YV, Kolomeichuk SN, **Cornelissen G**. Larger body mass index associated with sleep phase delay and low daytime skin temperature despite similar 24-hour patterns of physical activity in adults. *Journal of Chronomedicine*, in press.
22. Siegelova J, **Cornelissen G**, Havelkova A, Pohanka M, Dunklerova L, Dobsak P. Seven-day/24-h ambulatory blood pressure monitoring in night shift-workers in health service. *World Heart Journal*, in press.
23. Wilson DW, Halberg F, **Cornelissen G**, Singh RB. Chronoastrobiology in the context of Universal Biology. *World Heart Journal*, in press.
24. **Cornelissen G**. Centenary celebration of Franz Halberg, a maverick ahead of his time. *World Heart Journal*, in press.
25. Sackett-Lundeen L, Otsuka K, Havelkova A, Siegelova J, Beaty LA, **Cornelissen G**. *World Heart Journal*, in press.
26. **Cornelissen G**, Watanabe Y, Beaty LA, Turner AC, Sothorn R, Siegelova J, Breus T, Gubin D, al-Abdulgader AA, McCraty R, Otsuka K. As-one-goes blood pressure and heart rate monitoring: a chronobiologic approach with applications in clinical practice and basic science. *Heart and Mind*, in review (by invitation).
27. **Cornelissen G**. Circadian disruption and metabolic disease risk. In: *Functional Foods and Nutraceuticals in Metabolic and Non-Communicable Diseases*. Singh RB, Watanabe S, Isaza A (Eds.), submitted (by invitation).
28. Gvozdjáčková A, Navas P, Kucharská J, Sumbalová Z, **Cornelissen G**, de Cabo R, Mojto V, Rausová Z, Singh RB. Coenzyme Q10 in prevention and development of metabolic and mitochondrial non-communicable diseases. In: Singh RB, Watanabe S, Isaza A (Eds.) *Functional Foods and Nutraceuticals in Metabolic and Non-Communicable Diseases*, submitted.

29. Otsuka K, **Cornelissen G**, Beaty LA, Norboo T. Combined assessment of ToCA-MCI and CAVI cost-effectively predicts conversion from MCI to dementia in community dwelling elderly. Submitted for publication.
30. Otsuka K, **Cornelissen G**, Kubo Y, Shibata K, Mizuno K, Furukawa S, Ohshima H, Mukai C. Chronomics medicine in space: restored and amplified circadian rhythms of heart rate and heart rate variability in long missions on the International Space Station. *Chronobiology Int*. Submitted for publication.
31. Otsuka K, **Cornelissen G**, Kubo Y, Shibata K, Mizuno K, Furukawa S, Ohshima H, Mukai C. Role of infraslow oscillation of heart rate variability at night in adaptation to space environment studied during 12-month-long mission. *Chronobiology Int*. Submitted for publication.
32. Otsuka K, **Cornelissen G**, Kubo Y, Shibata K, Mizuno K, Furukawa S, Ohshima H, Mukai C. Nocturnal rest facilitates neuroplasticity in space in response to increased brain's salience network activity. Submitted for publication.
33. Gubin D, Neroev V, Malishevskaya T, **Cornelissen G**, Astakhov SY, Kolomeichuk S, Yuzhakova N, Kabitskay Y, Weinert D. Melatonin mitigates disrupted circadian rhythms and improves ganglion cells function in glaucoma. In preparation.

#### Abstracts

34. **Cornelissen G**. Should blood pressure threshold values be gender specific? 15th Annual University of Minnesota Women's Health Research Conference: Stigma, Racism and Women's Health.
35. **Cornelissen G**, for the BIOCOS Investigators and the Phoenix Study Group. Rhythm alterations as sensitive gauges of aging and cardiovascular disease. ICC10 - International Congress of Cardiology & Cardiovascular Imaging 26th -27th March, 2021. Dusit Thani Dubai Hotel- Dubai, UAE.