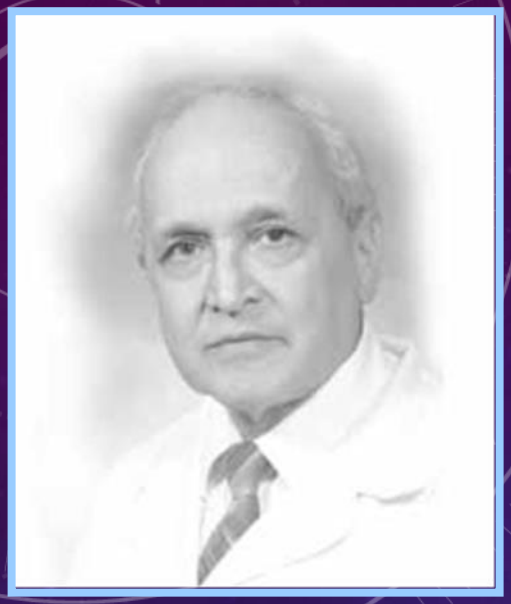


100th anniversary of the birth of Franz Halberg

July 5, 2019

30th meeting of the ISC
Warsaw, Poland

Motto:

"Measure what is measurable and render measurable in time what as yet is not"

BRIEF HISTORICAL BACKGROUND FROM ANTIQUITY TO 1937

Whereas cycles in biology have been reported by keen observers since Antiquity, the study of biological rhythms only started in earnest in the 1920s when a critical mass of integrated contributions from several investigators appeared, contrasting with the earlier publications that were isolated and sporadic.

To the mere description of periodicities, analyses of their structure and possible underlying mechanisms started emerging, recognizing the partly endogenous nature of rhythms.

This was the time when the study of rhythms became institutionalized. The Internationale Gesellschaft für biologische Rhythmusforschung was initiated in 1937 in Ronneby, Sweden, later becoming known as the Society for Biological Rhythms (SBR).

1971: BEGINNING OF THE ISC

One of the organizers of the SBR foundation meeting was the German physician Arthur Jores, future President of the Society. He was interested in practical aspects of rhythms from a therapeutic perspective, but he still viewed rhythms as being exogenous.

Cambrosio and Keating identified two stages post WWII critical to the development of chronobiology as a discipline in its own right: 1. Between the 3rd congress in 1949 held in Hamburg and the 9th meeting in 1967 in Wiesbaden, the SBR no longer monopolized events related to biological rhythms; 2. Starting at the 10th conference held in Little Rock, Arkansas, USA, in 1971, the first meeting in North America, the Society assumed the new name of the International Society for Chronobiology (ISC).

For the first time in 1953, American researchers attended the 4th meeting held in Basel, including **Franz Halberg**, who played a critical role in the transformation of the SBR into the ISC. Until 1960, the SBR remained primarily European with a strong interest in medicine.

CHRONOBIOLOGY AS A DISCIPLINE IN ITS OWN RIGHT

The year 1960 is considered a turning point in the history of chronobiology in view of the meeting in Cold Spring Harbor organized by Pittendrigh with Aschoff, Bünning and Bruce. Together with other meetings (e.g., 1957 in Gatlinburg, Tennessee on photoperiodism and related phenomena in plants and animals), research on rhythms was growing in the USA starting in the 1950s, centered mostly on circadian rhythms.

The dichotomy between the medical and biological approaches sharpened in the following years. In 1967 at the meeting in Wiesbaden, Jores named Halberg as his successor to the presidency. In 1971 when the SBR became the ISC, the Society explicitly adopted a disciplinary approach to the study of rhythms. In 1979, at the 14th Congress, the statement was formally made that “chronobiology should become an academic discipline in its own right” and was voted on as part of the Society’s constitution.

TWO CONTRASTING VIEWS

Pittendrigh considered that rhythms should be studied within the scope of their original scientific discipline, focusing exclusively on biological aspects of rhythms and their ‘clock” mechanism modeled by self-sustaining oscillators.

Halberg took a multidisciplinary approach, including problems of growth, development and senescence of interest to pediatricians and gerontologists within the scope of chronobiology, which he viewed as an integrated discipline like genetics.

Both men considered 1950 as the time of divergence between their respective approaches, albeit for different reasons.

This was the time when Halberg uncovered the circadian adrenal cycle and identified the adrenal as an anatomical entity, with known biochemical factors, capable of certain effects of a physiological nature, namely the depression of blood eosinophil counts.

COUNTING EOSINOPHILS, HALBERG SOLVED 3 PUZZLES, LEADING TO THE FOUNDATION OF CHRONOBIOLOGY

Franz Halberg could not confirm his unpublished results.

He had different results on the same groups of mice at different fixed clock hours because

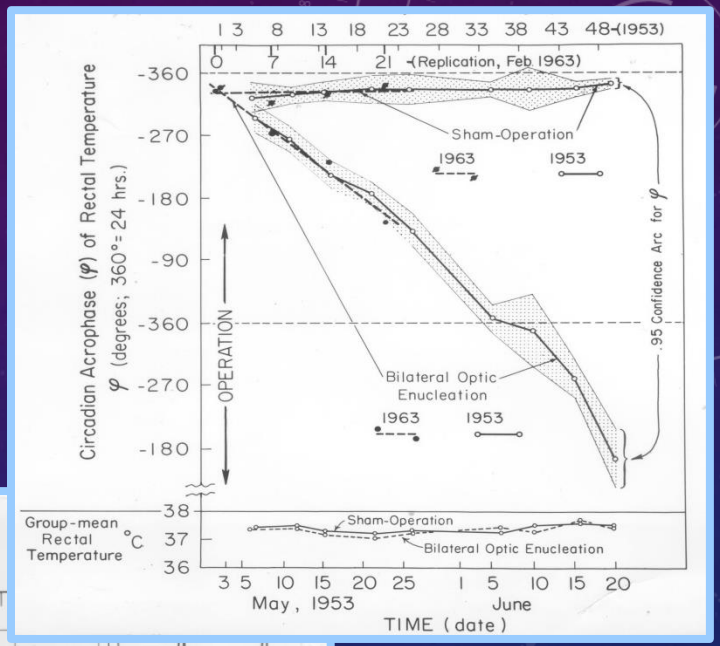
- Animals were phase-shifted;
- Animals were phase-drifting;
- Three puzzles had to be solved.

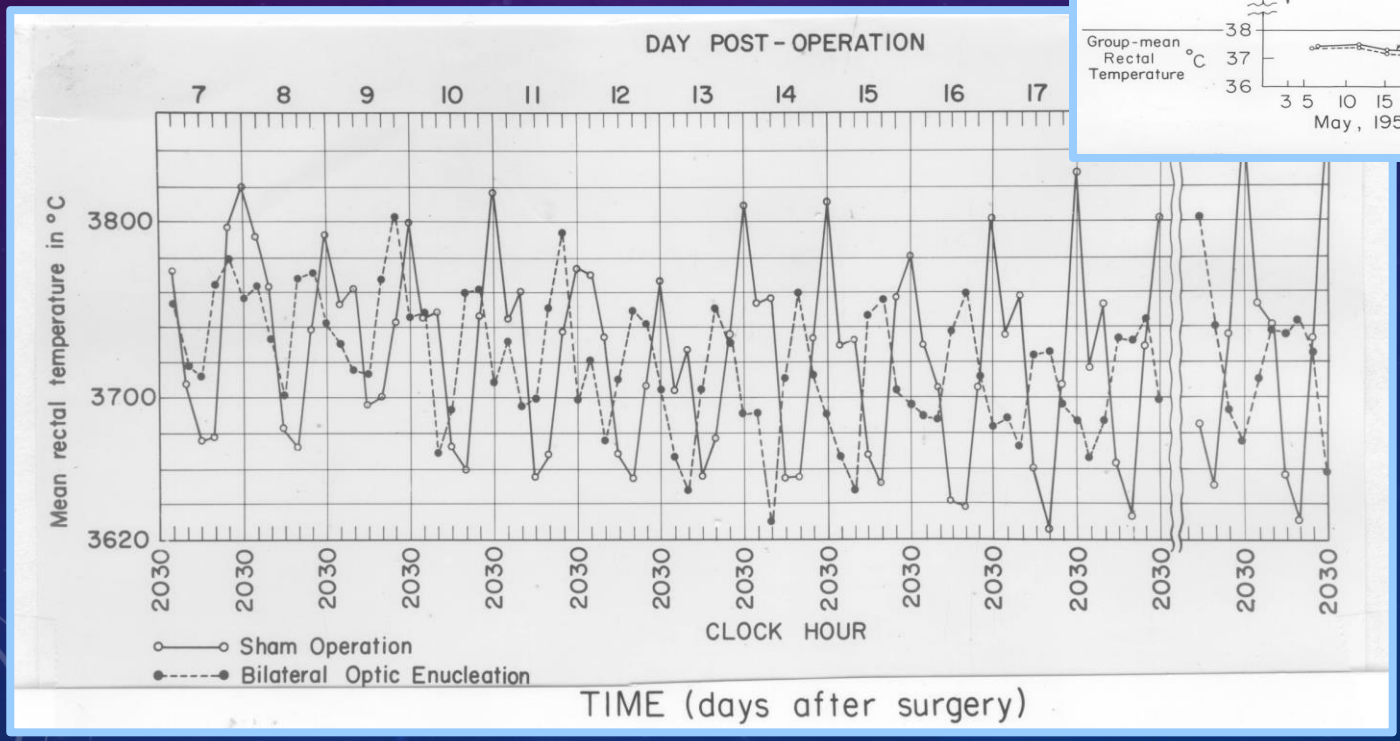
PUZZLES

- From Confusing Variability to Rhythmic Variation: From Foe to Friend: reproducible changes along the 24-hour scale
- Group Difference Reversals: Competing Environmental Synchronizers: the phase of circadian rhythms can be reversed by switching the lighting regimen from LD12:12 to DL12:12; time-restricted feeding to a single daily “meal” greatly alters the phase of some variables (insulin, glucagon, growth hormone) whereas the phase of other variables is barely affected (cortisol)
- More Reversals in Group Differences: in the absence of environmental synchronizers, physiologic variables continue cycling but with a period that differs slightly but statistically significantly from exactly 24 hours – free-running

FREE-RUNNING

Halberg realized that the information about the lighting regimen was transmitted to the hypothalamus through the eyes.
By monitoring blinded and control mice around the clock longitudinally, blinded mice were found to continue cycling but with a period slightly but significantly different from 24 hours.





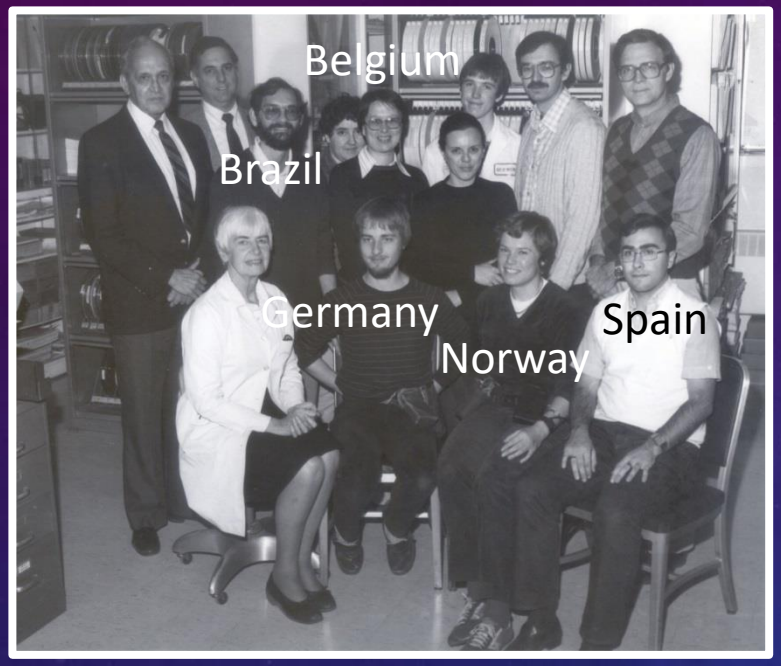
IMPLICATIONS

- If circadian rhythms are partly endogenous, they must be important.
- This is now recognized thanks to the discovery of clock genes present in almost every cell.
- These clock genes not only maintain a healthy time structure, but are also responsible for health.

HALBERG LOVED TO COIN NEW TERMINOLOGY

- **Circadian**: Term coined in 1959 by Franz Halberg at the University of Minnesota – defined as "Relating to biologic variations or rhythms with a frequency of 1 cycle in about 24 hours" – derived from Latin: "circa" (about) and "dies" (day)
- **Chronobiology**: defined as the "science objectively quantifying and investigating mechanisms of biologic time structure, including rhythmic manifestations of life".

HALBERG'S LIFETIME'S ACCOMPLISHMENTS ARE SUMMARIZED IN OVER 3,600 PUBLICATIONS IN COOPERATION WITH COLLEAGUES AROUND THE WORLD



MILESTONES

- Free-running implying endogenicity conveyed critical importance of circadian rhythms (before clock genes had been discovered!);
- Circadian Cell Cycle: demonstration of circadian variation at a time when RNA and DNA were regarded as constant, with the phase of RNA preceding that of DNA; circadian rhythm in mitosis laid the foundation for cancer chronotherapy;
- Susceptibility/Resistance Cycles underlie chronotherapy more generally – the organism's response to a given stimulus depends on the rhythm stage of its administration;
- Marker Rhythms-Based Chronotherapy: at the basis of personalized chronotherapy, demonstrated notably for the case of hypertension;

MILESTONES

- Cosinor Rhythmometry: originally developed for short and sparse time series, the technique has been extended to the study of longitudinal records spanning decades of around-the-clock measurements;
- Circadians in Early Forms of Life: in 1961, Halberg was first to report circadian behavior in bacteria kept in continuous darkness;
- Feedsidewards: modification of the response of one entity to another entity by a third entity;
- Collaterally Hierarchical Celluloneuroendocrine Mechanisms: the nervous system and the adrenal cortex are both rhythmic; each can be critical for one rhythm or another, but neither is indispensable for all rhythms. Halberg's vision is now being studied at the cellular and molecular levels;
- Partly Endogenous Circaseptan Rhythms.

HALBERG'S ENDEAVORS EARNED HIM MANY AWARDS

Franz Halberg and Thomas Kenner
Masaryk University, Brno, Czech Republic

Franz Halberg
Friendship University, Moscow, Russia

Among many other awards, 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).

IN INDIA, A HOSPITAL HAS BEEN NAMED AFTER HALBERG

FRANZ HALBERG (1919 – 2013)

Franz was a remarkable man and an exceptional scientist.

He is regarded by most as the “father” of modern chronobiology.

Having realized the critical importance and far-reaching implications of biological rhythms, he undertook the tasks of

(a) documenting their ubiquity at all levels of organization;

(b) developing methods for their objective and quantitative characterization;

(c) uncovering their rules of behavior and mapping a broad time structure of interacting multi-frequency rhythms;

(d) providing the nomenclature; and

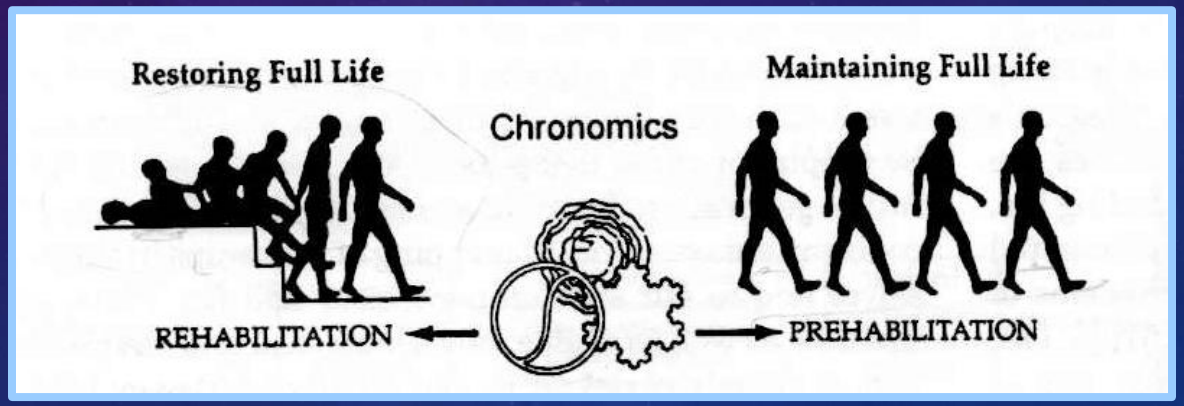
(e) paving the way for important applications in medicine and biology more generally.

AS WE CELEBRATE THE 100TH ANNIVERSARY OF FRANZ HALBERG'S BIRTH

We remember his incredible legacy.

Halberg's lifetime work helped change the world, and he was fortunate to witness the impact it made.

It now falls upon us to follow in his footsteps and teach the next generations the lessons learned with Franz throughout our lifetimes.



THANK YOU