

# Chronomedicine: An old concept's fledging? A selective literature search\*

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Aschoff; Lerner; Halberg; Pittendrigh**

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## Abstract

Chronomedicine may be conceptualized as dealing with the prevention, causation, diagnosis, and treatment of diseases in humans with a particular focus on the role "time" [Greek: chrónos] plays in our physiology, endocrinology, metabolism and behavior at many organizational levels. While it has been used as a term and somewhat pursued as a discipline for decades, it appears that chronomedicine has captured a broader interest as a promising specialty only more recently. This commentary addresses roots of chronomedicine in the 1900s and perspectives for chronomedicine in the 21<sup>st</sup> century. Classical terms of chronobiology, e.g., Zeitgeber, melatonin and circadian, may be traced back to Aschoff, Lerner, and Halberg, respectively, but who actually coined the term "chronomedicine" and used it first in a publication remains unclear.

Importantly, it could be (come) rather straightforward to transfer abundant insights gained from chronobiology to strategies in chronomedicine as animal models have been increasingly developed to understand human health and disease. Perspectively, chronomedicine should comprise "clinical chronomedicine" (individual-based) and "preventive chronomedicine" (population-based). Overall, due to the "maturing" of chronomedicine as a field, the near future might bring a section dedicated to chronomedicine in existing journals, or even a "*Journal of Chronomedicine*" as vectors of ideas and research.

\* Material used in this paper was synthesized in a poster presentation at the SLTBR meeting in Geneva, Switzerland, June 25-27, 2012.

## INTRODUCTION

Chronomedicine has been used as a term and somewhat pursued as a discipline for decades. However, it appears chronomedicine has captured a broader interest as a promising specialty only more recently. Chronomedicine may be conceptualized as dealing with the prevention, causation, diagnosis, and treatment of diseases in humans with a particular focus on the role “time” [Greek: *chrónos*] plays in our physiology, endocrinology, metabolism and behavior at many organizational levels.

This concise commentary has two objectives: (i) to address roots of chronomedicine in the 1900s and (ii) to identify perspectives for chronomedicine in the 21<sup>st</sup> century. Researching and synthesizing the origins of chronomedicine enables the appropriate recognition of groundwork and could help to avoid “re-inventing the wheel” pitfalls (Sanderson 2007).

A selective literature search conducted with regard to roots of chronobiology and chronomedicine in the 20<sup>th</sup> century via MEDLINE and the ISI WEB OF KNOWLEDGE evinced that classical terms of chronobiology, e.g., *Zeitgeber*, *melatonin*, and *circadian* may be traced back to Aschoff (Aschoff 1951; 1954), Lerner (Erren *et al.* 2008b; Lerner *et al.* 1958), and Halberg (1959), respectively.

### 1951

#### Aschoff coins “Zeitgeber”

- *Eine rein endogene biologische Tagesperiodik wird beim vollständigen Ausschluß äußerer „Zeitgeber“ auf die Dauer nicht phasenetreu zur Erdumdrehung ablaufen (Aschoff 1951);*
- *Zeitgeber für tagesperiodische biologische Prozesse können alle Vorgänge sein, die für den betreffenden Organismus reizwirksam sind. (Aschoff 1954).*

### 1958

#### Lerner *et al.* coin “Melatonin”\*\*

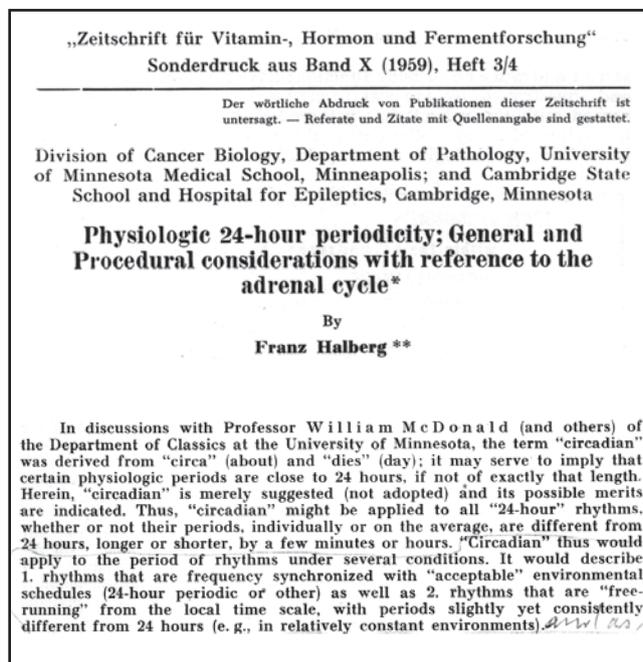
##### ISOLATION OF MELATONIN, THE PINEAL GLAND FACTOR THAT LIGHTENS MELANOCYTES<sup>1</sup>

Sir:

During the past forty years investigators have reported that injection of pineal gland extracts into tadpoles, frogs, toads and fish produces lightening of skin color.<sup>2-4</sup> Recently it was found that such extracts, by causing aggregation of melanin granules within the melanocytes of isolated pieces of frog skin, reverse the darkening effect of the melanocyte stimulating hormone (MSH).<sup>5</sup> We wish to report isolation from beef pineal glands of the active factor that can lighten skin color and inhibit MSH. It is suggested that this substance be called *melatonin*.

### 1959

#### Halberg coins “circadian”\*\*\*



Moreover, key roots with regard to chronobiology can be summarized as follows:

- A key defining event of chronobiology as a scientific discipline was the Cold Spring Harbor Symposia on Quantitative Biology in 1960 (XXV: Biological Clocks).
- Aschoff is considered one of the fathers of chronobiology.
- Halberg envisaged the direction of chronobiology with a focus on humans and medical applications (Halberg 1969).
- To Pittendrigh, however, it was pivotal to determine the interspecies evolutionary and ecological pathways of chronobiology.
- Jores, Menzel and Hildebrandt made contributions to “medical chronobiology” and “clinical chronobiology”, and to the “introduction of medicine to chronobiology,” respectively, (Lemmer 2009) in the 1900s.

However, the first to coin the term “chronobiology” and the first to use it in a publication, as well as the precise roots of the terms chronopharmacology and **chronomedicine**, remain elusive:

- The very term “chronomedicine” was used, and the discipline of chronomedicine as a whole was referred to, in publications decades ago.
- Identifying the specific roots and nestor(s) proves difficult: PUBMED and ISI WEB OF KNOWLEDGE searches of the word produced merely n=39

different hits between 1981 and 2011 in English (19), Russian (14), Chinese (3) and German (3). Examination of Russian texts suggested that the term appears to originate in the late 1960s to early 1970s in the former USSR.

## CONCLUSIONS

The questions “who” first suggested the term chronomedicine and “how” it should be pursued remain open. Insights to these open questions are welcome from others and may be sent to the NEL editor or us.

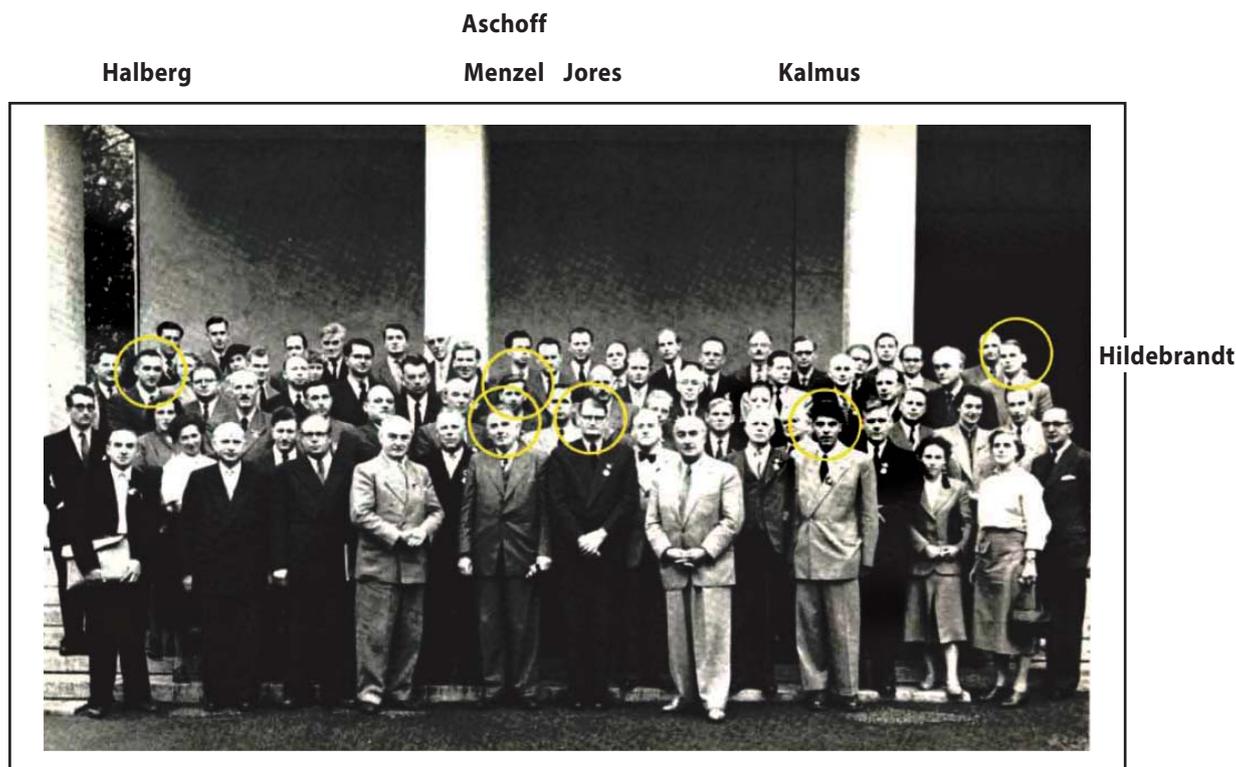
Although chronomedicine was used a mere 39 times since the 1980s in the peer-reviewed literature, this does not contradict our expectation that chronomedicine has prospect and potential as an emerging discipline. Importantly, in the field of chronobiology, animal models have been increasingly used and developed to understand human health and disease. Thus, it could be (come) rather straightforward to transfer abundant insights gained from chronobiology to strategies in chronomedicine.

In addition, there are practical indications of chronomedicine’s fledging: dedicated meetings have been held in recent years, including the 2012 Leopoldina symposium, “The Circadian System: from Chronobiology to Chronomedicine,” in Frankfurt, Germany (Korf 2012). Moreover, The European Biological Rhythms Society’s mission statement starts out with “EBRS aims to promote chronobiology and chronomedicine” (EBRS

2012). Perspectively, chronomedicine should comprise “clinical chronomedicine” (individual-based) and “preventive chronomedicine” (population-based).

At present, publications regarding interesting insights for chronomedicine, such as the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) (Science News and Editorial Staff 2002) or suggestions for a light-associated perinatal imprinting of circadian system stability (Ciarleglio *et al.* 2011) can be found in core interdisciplinary journals such as *Science* or *Nature*. Other facets of chronomedical relevance are published in specialized journals (Erren & Reiter 2008; Erren *et al.* 2010) which cover many links in the chains of causation that may be broken to promote health and prevent disease. To exemplify, causes of circadian disruption or chronodisruption are presented and discussed in occupational (shift-work) and environmental (light at unusual times) medicine journals and epidemiology journals; possible key intermediates such as melatonin are covered in neuroendocrinology (Erren *et al.* 2012a;b) and chronobiology journals; and endpoints such as cancer, sleep or mental disorders et cetera are published in multidisciplinary science (Erren *et al.* 2008a), cancer, oncology, sleep, and psychiatry journals.

Overall, due to the “maturing” of chronomedicine as a field, a section dedicated to chronomedicine in existing journals, or even a “*Journal of Chronomedicine*” as vectors of targeted ideas and research may be of interest. There appear to be good reasons that the near future could bring precisely that.



Basel, Switzerland 1953\*\*\*\*: 4th Conference of the International Society for Biologic Rhythm Research (Lemmer 2009).

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