Biological clocks and diseases

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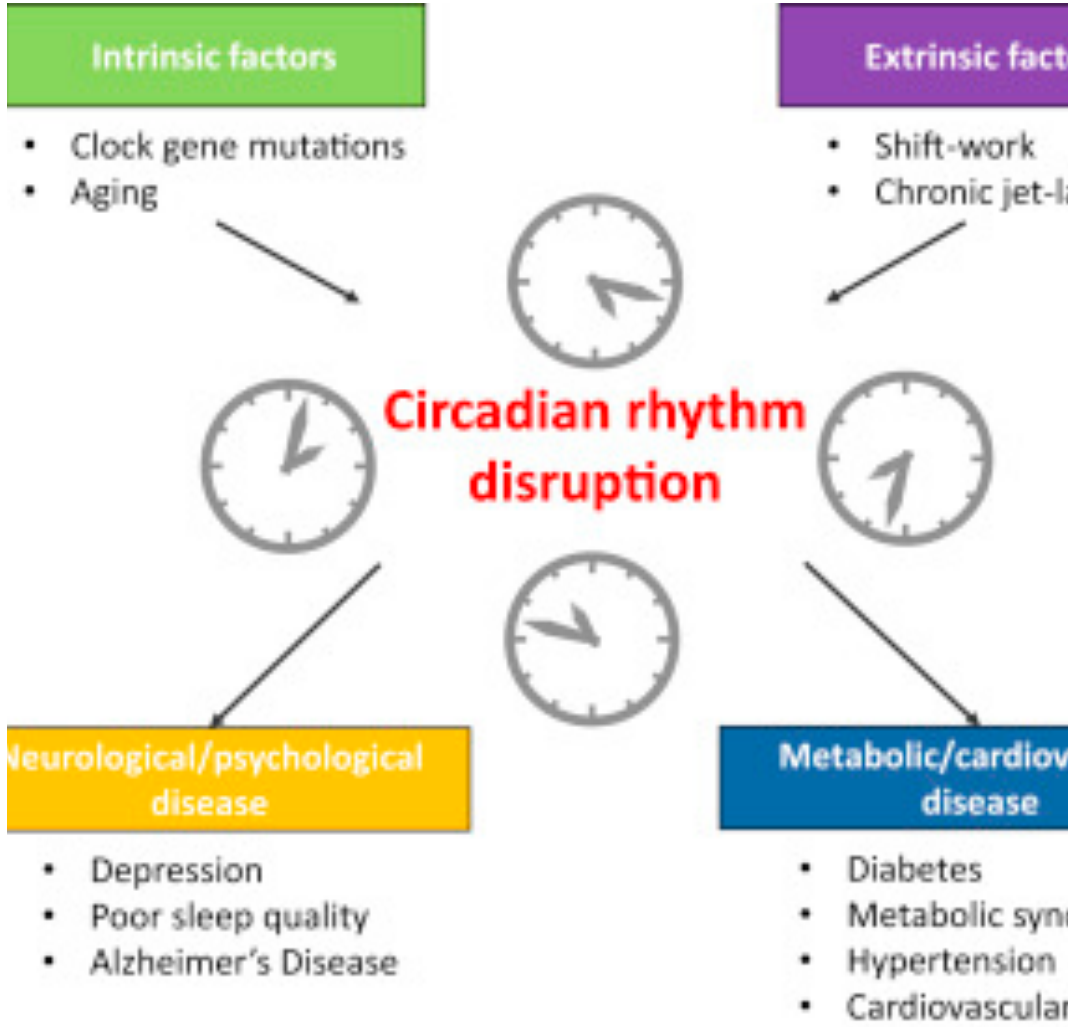
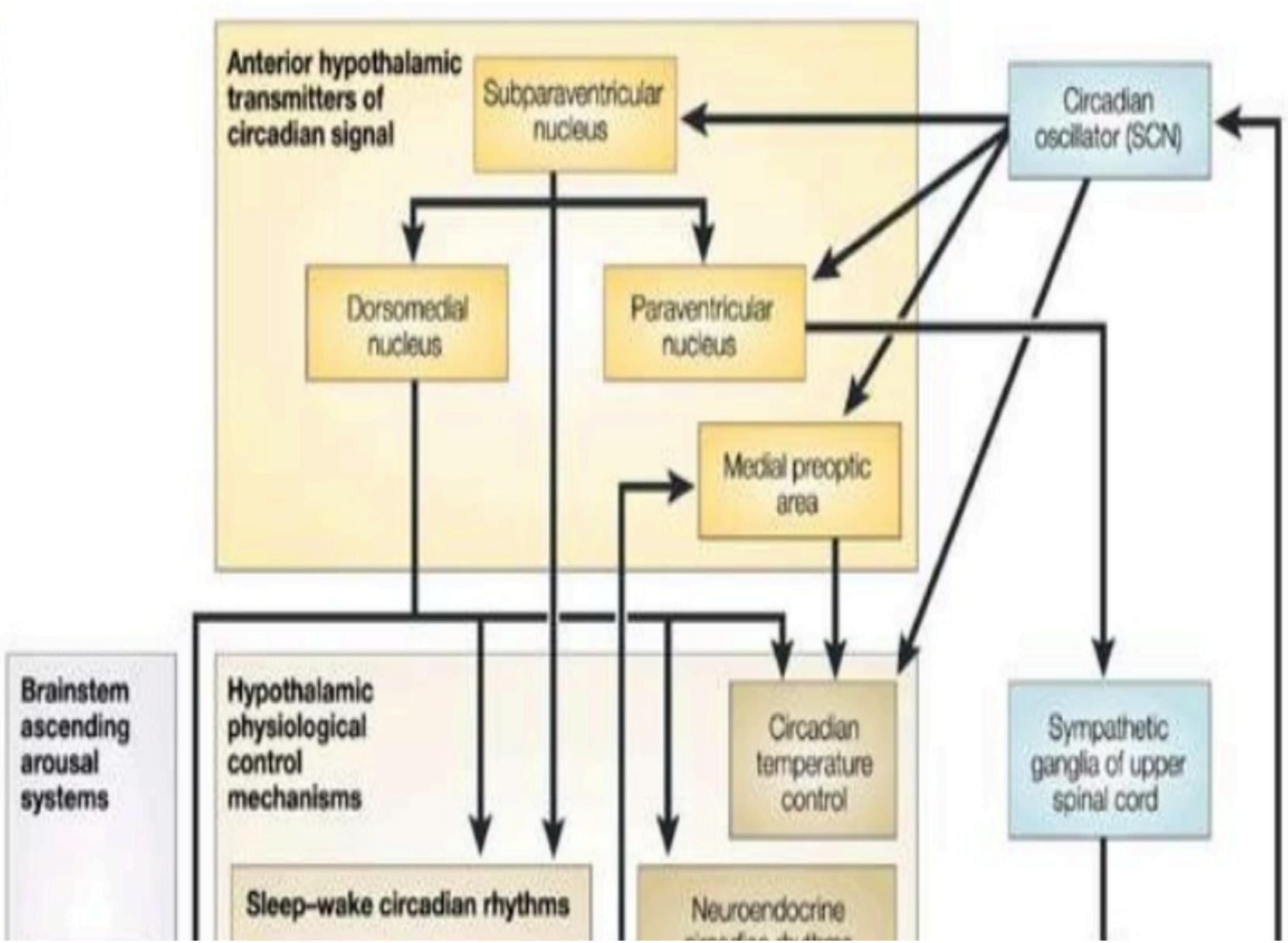
Prepared from interviews and reviews of lead chronobiologists

Introduction

Sehgal and Zhang, 2019. Circadian Rhythms and Disease in Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics. Editor(s): Reed E. Pyeritz, Bruce R. Korf, Wayne W. Grody, Academic Press, 299-314,

Life evolved with the 24-h rotation of the Earth. As a result, organisms have evolved ways to measure daily time intrinsically with circadian clocks, which allow for anticipation of events. Many changes to physical, mental, and behavioral state are governed by endogenous circadian clocks. As a result, disruptions of clocks, which can because by misalignment between the environment and internal clocks or dys-synchrony of clocks within an organism, can have pathologic consequences. We review here the impact of clocks on overall physiology and the relevance of circadian disruption to disease, with a focus on metabolic and neurologic disorders.




Anterior hypothalamic transmitters of circadian signal
Subparaventricular nucleus
Circadian oscillator (SCN)
Dorsomedial nucleus
Paraventricular nucleus
Medial preoptic area
Brainstem ascending arousal systems
Hypothalamic physiological control mechanisms
Circadian temperature control
Sympathetic ganglia of upper spinal cord
Sleep-wake circadian rhythms
Neuroendocrine

CLINICAL IMPLICATIONS OF BIOLOGICAL CLOCKS

- From the endocrinology and clinical medicine standpoints that the daily rhythms have long been known to be manifested in organismal physiology, compared to other fields of systems biology. discovery of the mammalian and fly circadian genes unveiled genetic mechanisms behind temporal processes. There is a crosswalk between metabolism and biological clock and these are intertwined at the level of basic property of homeostatic equilibrium in the body.
- Biological clocks have clinical implications, has long been known. but bodies work at molecular level is recent information revealed through functional genetic approaches. Studies on model species like cyanobacteria, drosophila, mice etc. have contributed to the knowledge of human circadian rhythm's for example, how feeding or other behavioural rhythms are associated at the level of temporal organization. Just as, Clock mutant mice, which had disorganized circadian sleep/wake behaviour, also gained weight if they were challenged with a high-fat diet. This finding suggested that the clock system and the related sleep/wake cycles it regulates might somehow intersect with the behavioural circuitry that controls weight homeostasis.

Bass 2016 Circadian time signatures of fitness and disease. Science;354(6315):994–9.

While concept of nutrient homeostasis sits at the basis of knowledge that nutrient systems control weight and that abnormalities in weight or obesity are due to an abnormality in these long-term homeostatic or short-term satiety systems. Chronobiologists started to think that sleep/wake behaviour and photoperiodism could be regulating fundamental nutrient responsive homeostatic systems. As they sought to genes that control behaviour related to feeding, molecular studies in terms of endocrine physiology viz. pathways controlling body weight, and transcription factors underlying the regulation of β-cell function became important. Now a days, use of approaches from next-generation sequencing have enabled testing how clocks exert these diverse control processes.

Bass 2016 Circadian time signatures of fitness and disease. Science;354(6315):994–9.

Taking example of insulin secretion and function

- This unit is specifically from focussed work of Joseph Bass at Northwest University, USA, who utilized his knowledge of the biology behind insulin production, and the genes that regulate physiology and biochemistry. The idea was that tits clock genes that encoded transcription factors must be involved in regulating insulin production in the pancreatic β-cells. He has proven that the clock system in the pancreas controls insulin secretion. The link between clocks and pancreatic β-cell function unveiled the mystery behind fundamental regulatory control of β-cells.

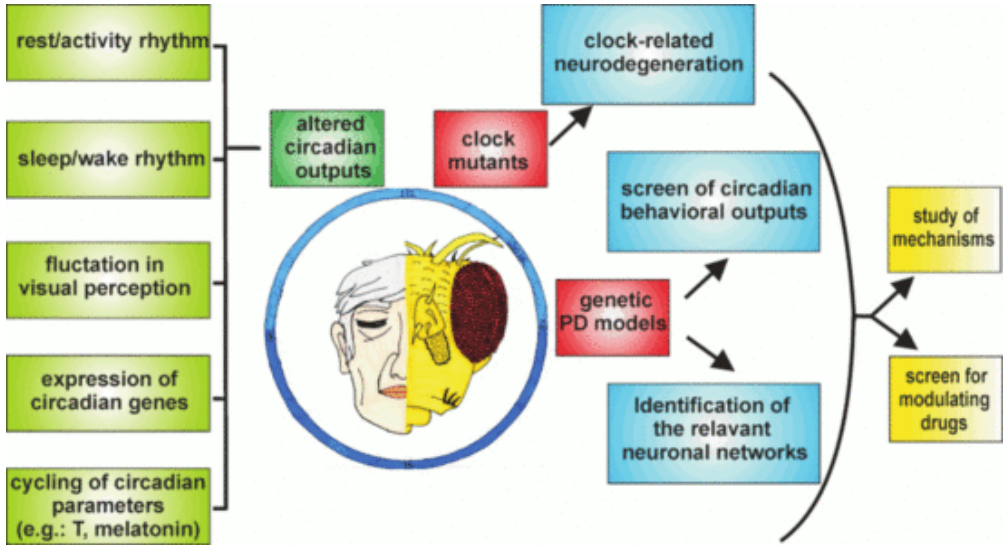
Bass 2016 Circadian time signatures of fitness and disease. Science;354(6315):994–9.

Drosophila, mice mutants and human clock studies

Benzer and Ron Konopka , working on Drosophila genetics showed that genes control behaviours including genes that control sleep/wake behaviour and encode transcription factors that operate through a feedback mechanism in the brain. The clock genes are widely expressed in every organism and present in nearly every cell throughout the body.

genetic studies in mouse started with mouse clock system genes. Almost all aspects of human life are now well investigated in mice through genetic mice using techniques like knock out etc.

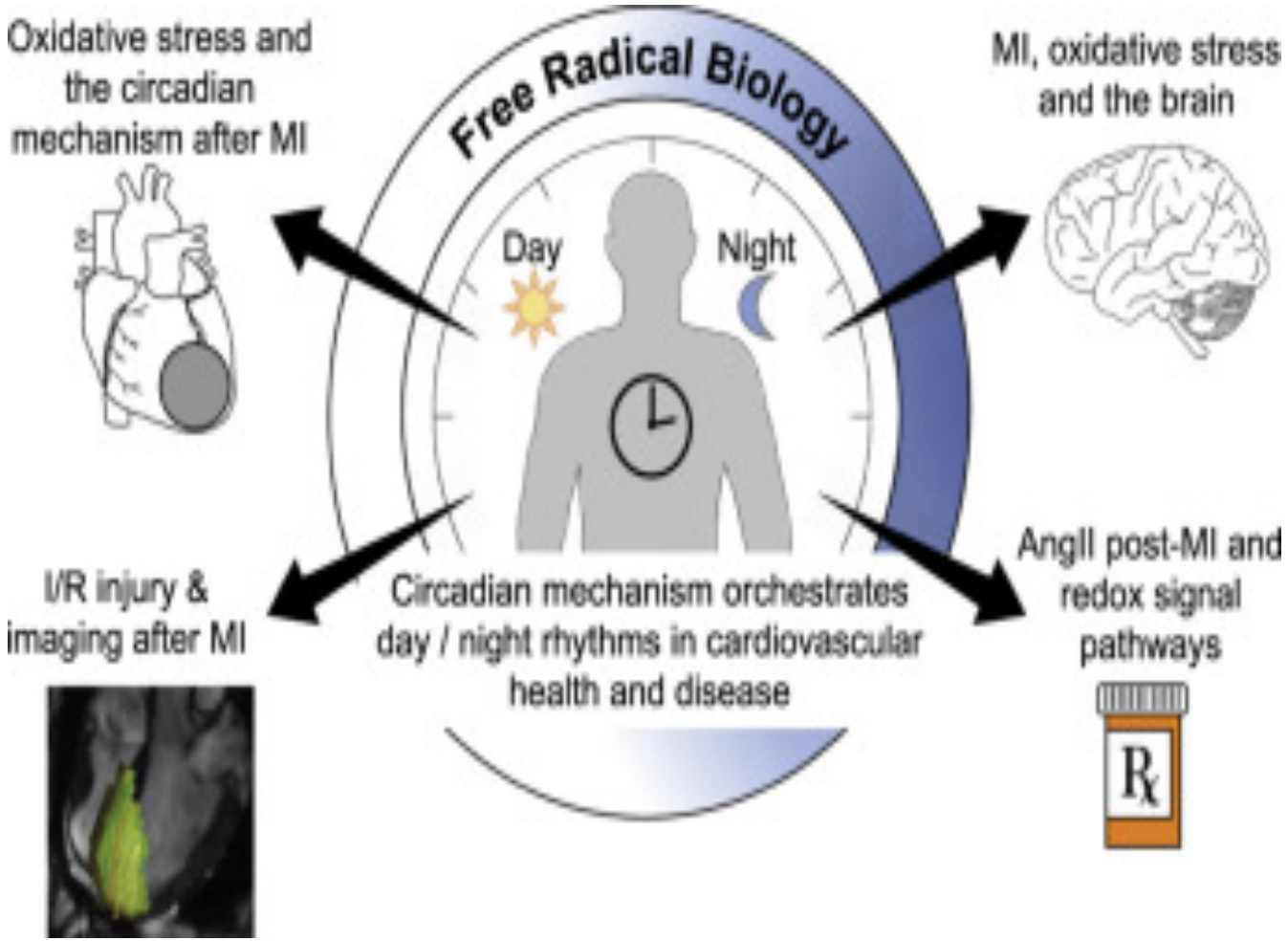
An example:



Circadian Rhythm Abnormalities in Parkinson's Disease from Humans to Flies and Back

De Lazzari et al Circadian Rhythm Abnormalities in Parkinson's Disease from Humans to Flies and Back. *Int. J. Mol. Sci.* **2018**, *19*, 3911.

Clinical and research studies have suggested a link between Parkinson's disease (PD) and alterations in the circadian clock. *Drosophila melanogaster* may represent a useful model to study the relationship between the circadian clock and PD. Apart from the conservation of many genes, cellular mechanisms, signaling pathways, and neuronal processes, *Drosophila* shows an organized central nervous system and well-characterized complex behavioral phenotypes. In fact, *Drosophila* has been successfully used in the dissection of the circadian system and as a model for neurodegenerative disorders, including PD. Here, we describe the fly circadian and dopaminergic systems and report recent studies which indicate the presence of circadian abnormalities in some fly PD genetic models. We discuss the use of *Drosophila* to investigate whether, in adults, the disruption of the circadian system might be causative of brain neurodegeneration. We also consider approaches using *Drosophila*, which might provide new information on the link between PD and the circadian clock. As a corollary, since PD develops its symptomatology over a large part of the organism's lifespan and given the relatively short lifespan of fruit flies, we suggest that genetic models of PD could be used to perform lifelong screens for drug-modulators of general and/or circadian-related PD traits.



Disturbing circadian rhythms (e.g. via shift work, sleep disorders) increases cardiovascular disease risk, and exacerbates cardiac remodelling and worsens outcome. Notably, reactive oxygen species (ROS) are important contributors to heart disease, especially the pathophysiologic damage that occurs after myocardial infarction (MI, heart attack)..

Circadian rhythms in the cardiovascular system have implications of rhythm disturbances in cardiovascular health. Free radical biology coincides with the pathogenesis of myocardial repair and remodelling after MI. studies indicate a role for the circadian system in the oxidative stress pathways in the heart and brain after MI. This fusion of circadian biology with cardiac oxidative stress pathways is novel, and offers enormous potential for improving our understanding and treatment of heart disease

Khaper, et al. 2018 Implications of disturbances in circadian rhythms for cardiovascular health: A new frontier in free radical biology, Free Radical Biology and Medicine, 119, 85-92,

At an epidemiological and clinical level, metabolic and endocrine systems are among the most overt in terms of the connection to a timing mechanism because glucose is metabolized differently in the day and night. Liver metabolism also varies during the day and night across many different pathways, including the detoxification pathways, the generation of sterols and other macromolecules, and the activation of mitochondria and the production of energy. All these processes are alternating by day and night, and this is controlled by the circadian clock. Shift workers are more susceptible to diabetes and there is also a correlation with body weight and sleep time—thus, there is a rationale for focusing on the endocrine system.

Bass 2016 Circadian time signatures of fitness and disease. Science;354(6315):994–9.

- There are many rhythmic events in the body- e.g. asthma, which exhibits a strong association with nocturnal events, or blood pressure control, which is also strongly rhythmic as it’s controlled through the hypothalamic–pituitary–adrenal axis. The hypothalamus controls the pituitary and the adrenal gland’s production of mineralocorticoids, which are also under rhythmic control, as is the autonomic nervous system.

Need for chronomedicine

- Now that there is enough applied chronobiology information and intellectual revolution, it hasn't yet translated into a therapeutic change because it's pleiotropic, affects many different processes, and it's a matter of working through where the system can be manipulated in such a way as to improve health in a certain disease.
- Another important area to mention is cell growth, immune signalling, and inflammation. These are all processes in which there are intersections with the clock, and even the basics of what we know about aging are interlinked with clock processes. Many different systems are affected; this is a conceptual entry point into a broad range of opportunities for understanding disease.

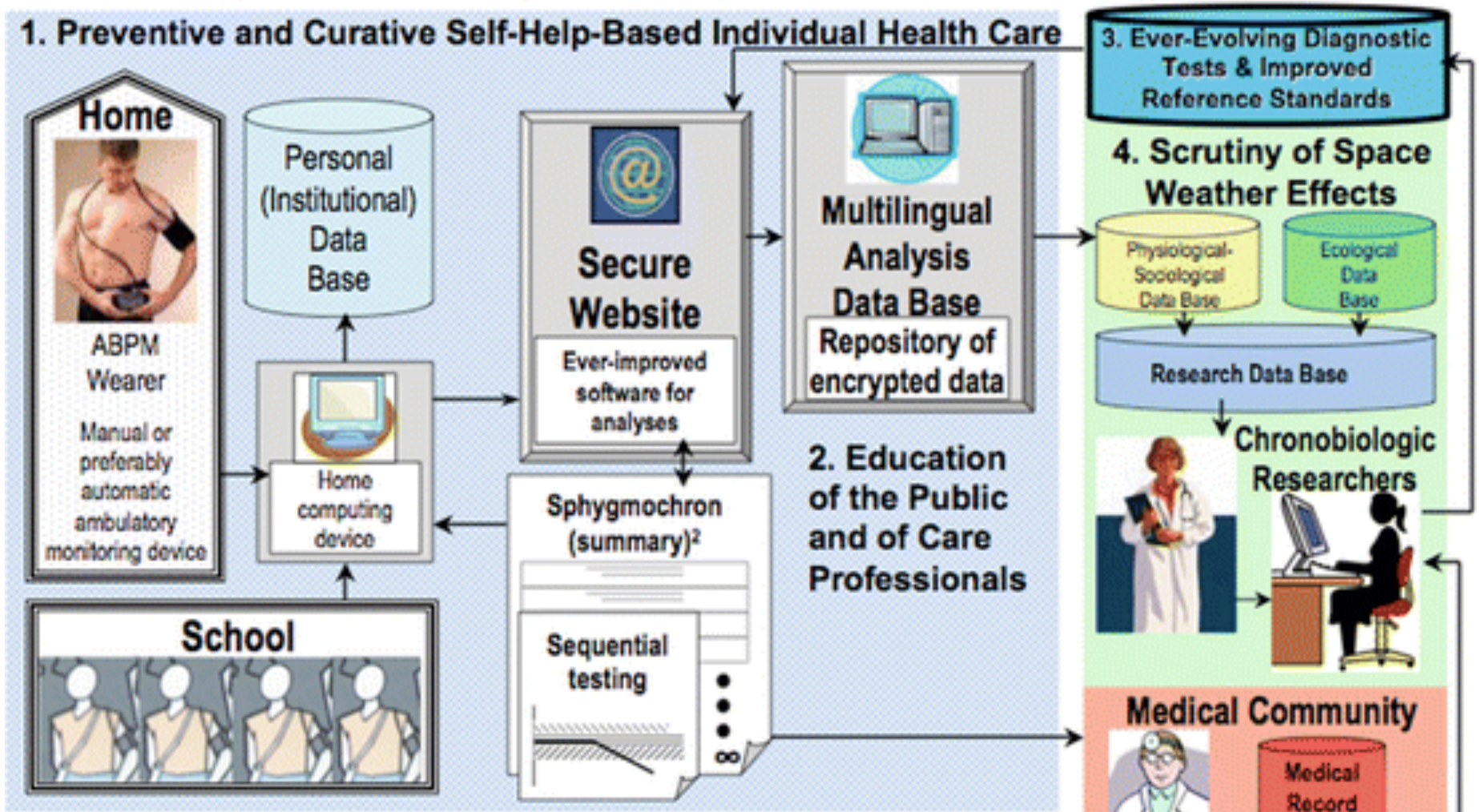
How mechanism behind these diseases are studied

- Scientists try to detect hormonal deficiency by challenging the axis required for a hormone to elicit an effect. For example, to investigate how the adrenal gland produces cortisol they can give the recombinant form of cosyntropin and look for stimulation.

- Franz Halberg (1919–2013) developed chronobiology and founded the field of chronomedicine including chronomics, chronoastrobiology, and chronobioethics. He coined the term circadian, after documenting that biologic rhythms tip the scale between health and disease and even between life and death. He showed that the large extent of cardiovascular variations can be exploited in the form of dynamic and other endpoints derived for each individual, for use in preventive as well as curative health care.

- An earlier paper by Halberg was labeled by the editor of the Journal of Gerontology A: Biological Sciences and Medical Sciences “Future history.” Halberg had fore seen circadian rhythms as the study of time structure in living matter (chronobiology) investigated in biological data. He interepreted that it may take another generation to develop a chronobiologically interpreted ambulatory blood pressure and heart rate monitoring (C-ABPM) system, which allowed mapping of infradian, e.g., paratridecadal cycles and perhaps some new information thereby concerning the health not only of individuals but also of societies, and may even detect the antecedents of earthquakes. We should be able to measure, as-one-goes, all rhythms that can form the basis of diagnostic and therapeutic measures. When known or assessed, such rhythms resolve effects of aging and are particularly indicated in view of the epidemic of noncommunicable diseases, referred to as a “slow-motion disaster” a aligned with space and other “weather” series (by chronomics).

g Preventive and curative health care can yield the dividend of biomedical monitoring of space weather by time-structural analyses of ambulatory blood pressure and heart rate series[1]



(1) by aligning longitudinal and linked cross-sectional biomedical with (whenever possible also local and global) physical environmental monitoring for transdisciplinary science -- while safeguarding anonymity, privacy and security with lifelong follow-up. • (2) If abnormal, participants are advised to allow data and analyses transfer to care providers for surveillance, diagnosis, optimization of treatment, if and as need be, and for ascertaining continued efficacy.

Modified from Figure 1 (Phoenix Architecture) in Adams C Privacy requirements for low-cost chronomedical systems. Int Conf on the Frontiers of Biomedical Science: Chronobiology, Chengdu, China, September 24-26, 2006, p. 64-69 , originally with Larry A. Beaty (www.sphygmochron.org) of the Phoenix Project (www.phoenix.tc-ieee.org/).

Aspects of the circadian clock implementation in medical practice?

Main applications of chronobiology are in preventative medicine, diagnostics, and molecular tools to intervene in metabolic and other systems. Example is a hospital settings where continuous tube feedings to critical acre patient is in conflict with the endogenous circadian program and that this exacerbates insulin resistance in response to tube feedings. There are intensive care unit, where drug or nutrient infusions are provided without consideration for the clock, leading to disorganization of the circadian alignment of different systems. This is an area that needs to carefully consider in clinical medicine because we are potentially exacerbating problems. One of the most promising targets is cryptochrome, which is the repressor protein in the clock and a good example of a druggable molecule. Some of the proteins in the core clock itself could be targets given the correct pharmacologic opportunity.

Bass 2019

Chronopharmacology

- Variation in drug administration according to bodily temporal processes. Here we keep in view the biological periodicities.

We should investigate under conditions in which the clock is directing a homeostatic process that can be tested through challenging that process. In chronopharmacology, time and the directionality of drug administration, is considered with respect to which arm of the homeostatic process being investigated. Another example is the regulation of glucose levels in the blood, and there are two conditions under which we can study it. One is in response to a glucose challenge where the pancreas must produce insulin.

The other is in response to insulin in which the pancreas must produce glucagon and other counter-regulatory hormones. So, to understand the alternating nutrient condition (which is either high or low glucose), we must challenge under conditions where the genes for the system are manipulated and the time of day is controlled. It's a challenge to figure out how to test the system properly.

Chronopharmacology describes how certain drugs are metabolized differently at different times of day and, therefore, it may be optimal when studying drug metabolism to test the levels of the drug at different times in the cycle and to take advantage of this information to adjust and manipulate drug dosing. There are other behavioural implications, such as for optimal performance in shift work. Shift work is the extreme that we are all familiar with, but there is also a form of shift work occurring in a much more insidious way in our own lives. Computer and electronic displays emit blue light that stimulates the photo-responsive part of the eye that sets the clock, so you don't have to work in a factory to experience the adverse effects of shift work or 'social jetlag'.

Impact of circadian clock research on understanding of diseases and its putative potential for the early diagnosis or better prognosis of disease?

- Identifying biomarkers that exhibit diurnal rhythmicity which may provide a signature, for example, of how the immune system functions or how well the body can burn energy at different times of day. for example, one of these is to notice when you feel tired during the day or when you experience changes in your sleep/wake behaviour or other patterns that you recognize as being daily routines. Another example is that there is a greater potential for the heart to have arrhythmias at certain times of the day in people at risk of arrhythmia. All these circumstances can now be understood within the rational framework that these are rhythmic processes that evolved in a 24-hour period long before the advent of modern life.

Bass 2019

Chronotherapy

Chemical approaches that identify, in an unbiased way, molecules that may restore the system to the setting in the event of an altered clock. As our understanding of how the clock controls basic processes will continue to evolve, as well as genome biology and its downstream effectors. We really don’t know the connectivity from the clock to all the other systems that it controls or what these connections are or how they respond under perturbed conditions. In the brain, we have very sophisticated tools to question how brain centres control all sorts of functions and to elucidate exactly the interactions of the clock systems with other pathways. It is a very rich interdisciplinary field, there are many talented investigators, and there are several angles that will provide exciting new insights in both the fly and the mouse systems. It will also provide insights into sleep, which is an area where we really don’t understand much about the molecular underpinnings but which will be hugely important to reveal.

Bass 2019