PROGRAMMA DI CRESCITA ENDOCRINOLOGIA SALUTE

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CHRONOAUXOLOGY

Chronomics: trends and cycles in growth and cosmos rather than secularity

Franz Halberg, Germaine Cornélissen, Roberto Salti, Federico Perfetto, Roberto Tarquini, Stefano Stagi, Dewayne C. Hillman, George S. Katinas, Willemijntje A. Hoogerwerf, Franca Carandente, Kuniaki Otsuka, Jerzy Czaplicki, Sergei M. Chibisov, Lawrence A. Scheving, Elena Vasilievna Syutkina, Anatoly Masalov, Gen Mitsutake, Zhengrong Wang, Chaomin Wan, Othild Schwartzkopff, Earl E. Bakken

EDIZIONI CENTRO STUDI AUXOLOGICI

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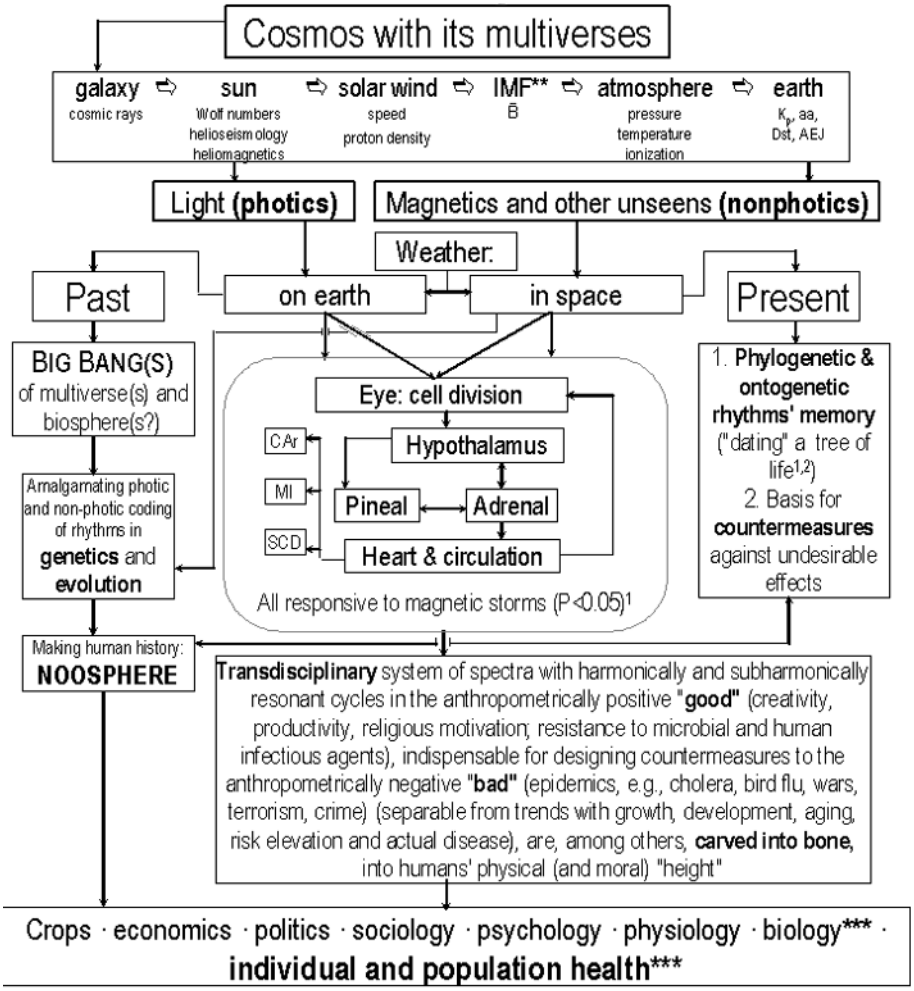
Contents

1. Preamble

Several aspects of growth exhibit cycles, some dealt with as secularity (Secular, 1965; Vercauteren, 1984; van Wieringen, 1986; Hauspie and Vercauteren, 2004; De Michelis and Cafarella no date; Secular no date). Nations and populations, like growth, depend upon their cosmos via photic, readily perceived mechanisms and via non-photic, mostly unseen influences, invisible except for the aurora. Partly magnetic cycles are found with many periods (among others!) of about (~) half a week, ~ a week, ~ a month, ~ a year, ~ a near-transyear (longer than a year by a few weeks) and often several far-transyears (e.g., ~15 and/or ~18 months long), and ~ a decade two and/or three, as are the Schwabe, Hale or Brückner cycles of solar activity. The latter are gauged by all positive Wolf's relative sunspot numbers (WN) (the Schwabe cycles), or WN changing sign from negative (in odd-numbered solar cycles) to positive (in even-numbered solar cycles) (Bracewell, 1953) or by solar flares. With their harmonics and subharmonics, these cycles, partly built into organisms, resonate with reciprocal cycles in the environment near and far (Halberg et al., 2004a and b). Long-known cycles in light, temperature and the climate, acting via crops, are not the sole influencers of economics and politics, and of what we know, the noosphere. By inferential statistics with the uncertainties involved and with a greatly extended scope, we resolve part of "secularity" into cycles. Far beyond the nutrition of a given generation, presumably the original implication, the following citation gains new substance in Scheme 1: "the growth of children [and, we add, the size of adults] amongst the various groups that make up a contemporary society reflects rather accurately the material and moral *[sic]* conditions of that society" (Tanner, 1986). Non-photic cycles of solar and galactic activity that qualify such statements are resolvable in growth and beyond with the 95% confidence intervals of their periods, amplitudes and phases. To our knowledge for the first time, we here testably postulate that the response to a non-photic factor, a magnetic storm, involves cell division in the eye (cornea), with this organ constituting a receptor perhaps of magnetics (as well as of light), while the same corneal epithelium constitutes a model for tissue and an eminently circadian periodic aspect of growth. The non-photic effect (of magnetic storms) can also involve the amplitudes and MESORs of circadian rhythms in melatonin of the mammalian hypothalamus and pineal (Zeman et al., 2005), the circulating corticosterone rhythm of the adrenal (Jozsa et al., 2005), the circulation (Otsuka et al., 2001; Watanabe Y et al., 2001; Cornélissen et al., 2002a; Oinuma et al., 2002) and blood pressure (Breus et al., 2002; Chibisov et al., 2004). A broad spectrum of cycles in human growth is a feature of our innate nature, not only, as is too commonly assumed, solely a function of nurture.

The photic mechanisms underlying the (harmonically and subharmonically resonant) cycles indeed affect mortality, as documented for the biological calendar year already by Quetelet in 1835, providing useful partial information, even though by

Scheme 1 - "Secularity" resolved by chronomics* into a transdisciplinary system of reciprocal cycles and trends revealing the dynamic of growth and its modulation by the cosmos.



*Chronomics complementing genomics resolves cycles, trends and chaos into rules (nomos) of time (chronos) structures, i.e., chronomes · **Interplanetary magnetic field · ***Rounded box refers to recently documented non-photic effects of magnetic storms in addition to effects on pathology, i.e., cardiac arrhythmia (CAr), myocardial infarctions (MI) and sudden cardiac death (SCD)

[1]J Applied Biomedicine 2006; 4:1-38 & 73-86; [2]Biomedicine & Pharmacotherapy 2004; 58 (Suppl 1): S1-S11.

stacking the data for a year, transyears (longer than a year) cannot be examined. Thus, we also warn against exclusive reliance on data stacking along the scale of the seen seasons or clock-hours: the actual cycles involved can free-run from these environmental lengths. At least equally important for non-photic effects is that, like growth, natality, mortality and, most importantly, perhaps morality (Starbuck et al., 2002) are all involved and resolvable in spectra of rhythms (Halberg et al., 2006a and b). The fact that the decadal or didecadal cyclic time structures are "carved" into our and our predecessors' bones renders them measurable and perhaps eventually manipulable not only for auxology but broadly in dealing with diseases of society and eventually in treating the bad (evil) and enhancing the good, so as to delay the now also documented cycles in the extinction of genera (Cornélissen et al., 2005; Rohde and Muller, 2005), at least insofar as humans are concerned.

If rule 1 of a chrono-ecology was the likelihood of built-in biotic periods for most consistent physical environmental periods, a second rule will emerge herein on which a series of tentative hypotheses can be built. For each consecutive period in the biosphere obtained with serially independent sampling as to individuals, we can seek an approximate longitudinal counterpart by repeated measurements on the same individual(s). This about 30-day period was first found transversely and then longitudinally in human dimensions at birth.

2. Historical background

Johann Gregor Mendel's studies on plant hybridization were ignored for decades. So now are Alexander Leonidovich Chizhevsky's (1968) studies of pervading effects of the sun, rightly revered in Russia and with notable exceptions elsewhere (Chizhevsky, 1934, 1938; Ertel, 1991, 1994, 1996; cf. Mikulecky, 1993, 1994, 1997; Mikulecky and Duris, 1998; cf. Sutcliffe and Duin, 1992; Halberg et al., 2005b); neglect continues, even though the proposition of solar effects is particularly supported by findings of pediatric associations with solar activity, including human growth (Cornélissen et al., 2003). Also ignored is the periodicity of mitosis and of DNA formation, dating back to the beginning and middle of the 20th century, respectively. Figure 1

Mendel's work led to genetics, the study of biological diversity in space, which in turn led to chronobiology, the study of diversity in time (Cornélissen and Halberg, 1994; Halberg et al., 2003a). As to "so what", chronomics led to the detection of treatable variability disorders carrying a risk greater than hypertension, a task not yet matched by genomics. As to growth, the timing of radiotherapy has helped double the 2-year survival rate of patients with perioral cancers (Halberg, 1967; Halberg et al., 2003b). We here touch on aspects of studies on time structure and timing that relate to growth in health, i.e., to auxology.

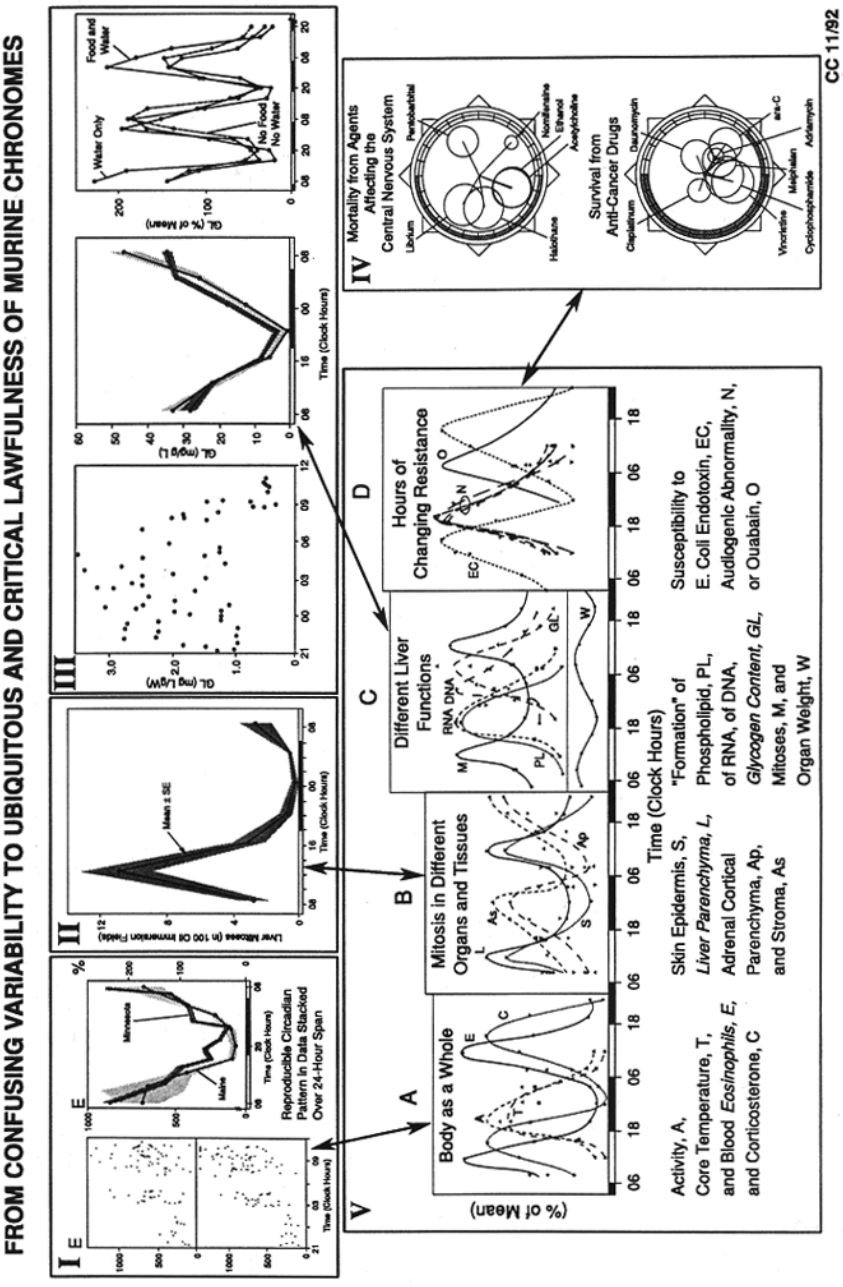

FROM CONFUSING VARIABILITY TO UBIQUITOUS AND CRITICAL LAWFULNESS OF MURINE CHRONOMES
I
II
III
IV
V
A
B
C
D
Body as a Whole
Mitosis in Different Organs and Tissues
Different Liver Functions
Hours of Changing Resistance
Time (Clock Hours)
(% of Mean)
Activity, A, Core Temperature, T, and Blood Eosinophils, E, and Corticosterone, C
Skin Epidermis, S, Liver Parenchyma, L, Adrenal Cortical Parenchyma, Ap, and Stroma, As
"Formation" of Phospholipid, PL, of RNA, of DNA, Glycogen Content, GL, Mitoses, M, and Organ Weight, W
Susceptibility to E. Coli Endotoxin, EC, Audiogenic Abnormality, N, or Ouabain, O
Mortality from Agents Affecting the Central Nervous System
Survival from Anti-Cancer Drugs
Reproducible Circadian Pattern in Data Stacked Over 24-Hour Span
Water Only
Food and Water
No Food No Water
CC 11/92

Figure 1 - From confusing variability to the ubiquitous and critical lawfulness of murine chronomes, i.e., time structures, sometimes in part apparent to the naked eye, best resolved time-microscopically. Time plots of original values (dots) of variables such as blood eosinophils (E), I, left, or glycogen content, III, left, reveal great variability, confusing at first, until the data are processed by relatively simple statistical techniques such as averaging and stacking over an idealized 24-hour span corresponding to an anticipated periodicity. Once this is done and the results are displayed as a function of time, they show the time-macroscopic ubiquity of circadians. The circadian variation in blood eosinophils determined years apart in two laboratories as far apart as Minnesota and Maine is closely reproduced (I, right). The lawfulness of the circadian variation yielded by the application of chronobiologic techniques is also revealed for the drastic changes in liver glycogen content, III, middle. A circadian rhythm in the liver's glycogen persists under conditions of starvation and dehydration, with little if any alteration in the dynamic rhythm characteristics, as compared to usual ad lib conditions, once the data are expressed as a percentage of the overall mean, III. The data averaging for different hours of the day also reveals differences in the time course (in phase) of different functions of a given organ such as the liver, VC, of cell division (mitosis) in different organs and tissues, VB, and of different variables at the level of the body as a whole, VA and D (Cornélissen and Halberg 1994).
After a prominent circadian rhythmicity was found at different levels of organization, several series of experiments were carried out under rigorously standardized laboratory conditions in order to investigate the effect of a single physical stimulus such as exposure to noise. Outcomes were as different as no response, convulsion or even death, as a function of the circadian stage at which the organism was exposed to noise. Whether the stimulus was audiogenic or the exposure to an endotoxin, or to a drug such as ouabain, or to whole-body irradiation, predictable changes were found as a function of the circadian stage at which the stimulus was applied, albeit with differences in the timing of these susceptibility-resistance rhythms to different agents. The hours of changing resistance were thus uncovered, and the times of overall largest response by the organism to a fixed stimulus applied at different rhythm stages mapped, VD. Applications followed. Prominent susceptibility rhythms were documented in the experimental laboratory, as illustrated here for the case of the mortality from agents affecting the central nervous system and for the case of the survival from (tolerance of) toxic doses of anticancer drugs. In each case, the nonoverlap by the elliptical 95% confidence region of the center of the circular plot (pole) can be interpreted as the presence of a statistically significant circadian rhythm in the susceptibility of the organism to each of these different agents. The orientation of the directed line (vector) indicates the time of acrophase, that is the time of the largest anticipated response (Cornélissen and Halberg 1994). Such charts are helpful in guiding the timing of the administration of the various agents so mapped. The chronotherapy of cancer is one critical application resulting from this work (Halberg et al. 2003b). © Halberg.

Growth in length constitutes a clear trend with superposed features dealt as secularity.[1] The widespread use of that word implies that leaders in the field knew it: there is more to know about the dynamics of this phenomenon in auxology than an increasing trend (Tanner, 1966, 1981; Nicoletti et al., 2004, 2006; see also Bransby, 1945; Eveleth and Tanner, 1990; Nylin, 1929; Orofsky, 1979; Roche, 1992; Otto and Reissig, 1963; Sutcliffe and Duin, 1992). Cell division, essential to growth, like many other phenomena, undergoes rhythms.

The daily change in mitotic count can drop to near zero, unless colchicine is used to trap mitoses. Thus, within each of several consecutive weeks at a young age, at least in one mammalian organ examined thus far the liver, the within-day change by far exceeds the extent of concurrent decline in mitotic rate with age. Any effects of therapeutic or other agents are best assessed at the peak time of the circadian rhythm, as reported for the pituitary growth hormone, GH (Halberg et al., 1973). The effects of a hormone at different circadian rhythm stages can not only be present vs. absent, (Halberg et al., 1973), but can be opposite, with respect to DNA labeling in bone, only as a function of timing along the 24-h scale (Walker et al., 1985; Cornélissen and Halberg, 1994).

Along with trends as one obvious element of time structure related to growth, a second element is a spectrum of multifrequency rhythms, much broader than a circadian system, only alluded to here, but to be kept in mind for the future. All these cycles are confounded, of course, when they are ignored and dubbed "secular" trends or variations.

In addition to trends and rhythms, a third element in any time structure is, verbatim, chaos in the broadest as well as the mathematical sense of chaos theory, Figure 1. Growth, in its very basic aspects, can be viewed as chaos, which can generate rhythms (Gonze et al., 2004; cf. Lloyd, 2005). Mammalian data to be considered here are neither dense nor long enough to deal with any nonlinearities of chaos, albeit by inferential statistics, an ever-present variability from unknown

1 There are "secular" trends and cycles, and there is certainly secular noise, with "secular" being used instead of a specification of any duration for either trend or cycle. Moreover, "secular" is defined differently in various fields. According to Tanner (1981, p. 116): "The increase in size seen in children, and seen to a lesser degree in mature adults, has become known as the 'secular trend'. This rather curious phrase denotes both the tendency to get larger and the tendency to become more early-maturing, tendencies which are usually, though not invariably, linked."In geomagnetics in turn, 'secular variation' is attributed to all the field variations that occur in periods of time between a decade and some hundreds [of] thousands of years" (De Michelis and Cafarella, no date). Merriam-Webster Online Dictionary (http://www.m-w.com/cgi-bin/dictionary, definition of secular) adds an even broader definition: "3 **a:** occurring once in an age or a century, **b:** existing or continuing through ages or centuries, **c:** of or relating to a long term of indefinite duration" (and Webster's Third New International Dictionary, 1965, p. 2053, adds to this the synonym "CYCLICAL"). The last adjective leads to transdisciplinary cycles. As a complement, and whenever possible as an alternative to secularity, we analyze, with an inferential statistical approach chronomes, time structures that numerically separate trends from rhythms with special reference

to reciprocal cycles in organisms and their environment (Halberg et al., 2000b, 2004). We do this beyond Quetelet's (1842; cf. 1835) separation of the influences of age, years and seasons; we also include non-stationary aeolian trans- and cis-years uncovered not only in the solar wind (Richardson et al., 1994; Mursula and Zieger 2000) but also in biology (Halberg et al., 2003c, 2004), now confirmed and extended to birth statistics (Cornélissen et al., 2005; Matuska and Mikulecky, 2006; Mikulecky and Florida, 2005).

Studies on time structures of growth, development and aging will eventually have to be, at least in part, **longitudinal** and individualized. Ideally, each person contributes, preferably automatically, dense around-the-clock serial data as a function of time -- covering decades, or at best a lifetime. Santorio Santorio (1657) began decades-long measurements of his own weight, but his actual measurements are unavailable. Time series on vascular and other variables are now available for decades in over a dozen "test pilots" and cover up to 38 years (Sothern et al., 2005; Halberg et al., 2006a and in press) so that one can examine whether they yield features that confirm, or are at least in keeping with the findings based on a **transverse**, i.e., cross-sectional approach when each individual contributes only a few, or even just one value, such as body length or weight that can be one of a kind if taken at a fixed time of life such as birth, or when, in a population, an event unique for the given individual, such as natality and mortality, is being investigated. Third, there can be a combined transverse and longitudinal (linked cross-sectional) dubbed **hybrid** design that samples repeatedly and longitudinally on several individuals and then prepares a summary of parameters from each member of the group. In the latter design, neither the length of each single series nor the number of individuals needed transversely may suffice in itself to draw certain validatable inferences, but the combination of results from such imputations (Halberg et al., 1967) may nonetheless allow the drawing of conclusions.

Also, when the longitudinal and the transverse sampling are each conclusive in their own right, an interpretation based on both of them has merit in concurrently considering problems relative to the health of individuals and populations. Thus, by focus upon cyclicity (always to be given with its indispensable uncertainty) in addition to any trends, chronomics, the study of time structures, resolves an otherwise confounded "secularity". This endeavor underlies an interpretation followed herein, toward building a time horizon from current, still limited longitudinal studies in the context of much earlier work on the same problem on populations, with particular reference to human growth parameters, some of which, at both the light-microscopic and time-microscopic levels, are more readily assessed by separating at least cyclic aspects and trends from noise, if not chaos, rather than confounding these two aspects as "secular" (Hauspie and Vercauteren 2004; cf. Tanner 1966; Vercauteren 1984; van Wieringen 1986; Eveleth and Tanner 1990).

Series of body weight and length at birth analyzed for groups as a function of time reveal a spectrum of rhythms, probably anchored in the gene pool of the population, but also critically dependent upon nutritional and thus upon economic factors, and all of them dependent directly or indirectly upon photic and/or non-photic effects of the sun. Cosinor assessment (Halberg 1980) of components in hybrid time series in relation to different reference standards assesses complementary contributions by "nature", as prenatal experience including genetics, and "nurture" as complex postnatal epigenetics i.e., in appearance (phenotype) as gene expression by mechanisms other than the chargesin the urnderlying sequence. Among others, some rhythmic spectral components widely differing in frequency, involved in body weight and length and in head, chest and abdominal circumference are here analyzed, as hints of cosmic effects based on time series covering 100 years or more. The complementary hybrid interpretation of transverse and longitudinal data provides a broader-than-usual time horizon for investigation of the mechanisms involved in cycles of growth along all of the scales of spectral elements in chronomes.

An as-yet unexploited timing of hormone administration by scholars of growth, taking about-daily and about-weekly cycles into account, could be an immediate practical result of chronomes in auxology. The manipulation of the magnetic environment, notably of the newborn, could be a later addendum to heating and air conditioning of critical care units.

sources has to be taken into account. We focus, with trends, upon multifrequency rhythms that constitute a spectral element in time structures, or chronomes (from *chronos* = time and *nomos* = rule), Figure 2 (Halberg et al., 2001a, 2003d) and Table 1. Historically light-microscopy revealed variability in mitoses and was resolved first, time-macroscopically, as to its about 24-hour rhythms, mostly by descriptive statistics. About 24-hour rhythms in mammalian liver were recognized as a built-in cell cycle leading to mitosis (Barnum et al., 1958; Halberg et al., 1958; Cornélissen and Halberg, 1994). Auxology, like medical science as a whole, need not, by implication if not explicitly, use homeostasis as a shield to keep alive the misconception that cell division occurs at random, also underlying many studies that focus only on up- or down-regulation as an excuse for ignoring rhythms and thus as an opportunity for gravely misleading blunders.

In the past half-century, about-half-weekly and about-weekly cycles, among other infradians, were found to characterize growth (Halberg, 1995, 2000). About-didecadals became recognized as components in spectra of variables of populations relating not only to neonatal length and weight, but also to head, chest and abdominal circumference, based on data covering 112 years (Halberg et al., 2001b; Cornélissen et al., 2003). In cases examined thus far, the amplitudes of the didecadals exceeded those of the circannuals. Most recently, we detected, in a longitudinal 38-year series

Figure 2 - Measurable time structure (chronome) of a variable. The chronome (derived from *chronos,* time, and *nomos,* rule) represents quantitatively the measurable time structure of any variable, biological or environmental. In biology only, the ending "-ome" can also stand for "chromosome", to convey the genetic basis of (habitat- and broader cosmos-influenced) multifrequency rhythms, which are the major elements of chronomes, along with developmental and other age trends, and chaos, all interacting as feedsidewards among different frequencies in us and in our environment. © Halberg.

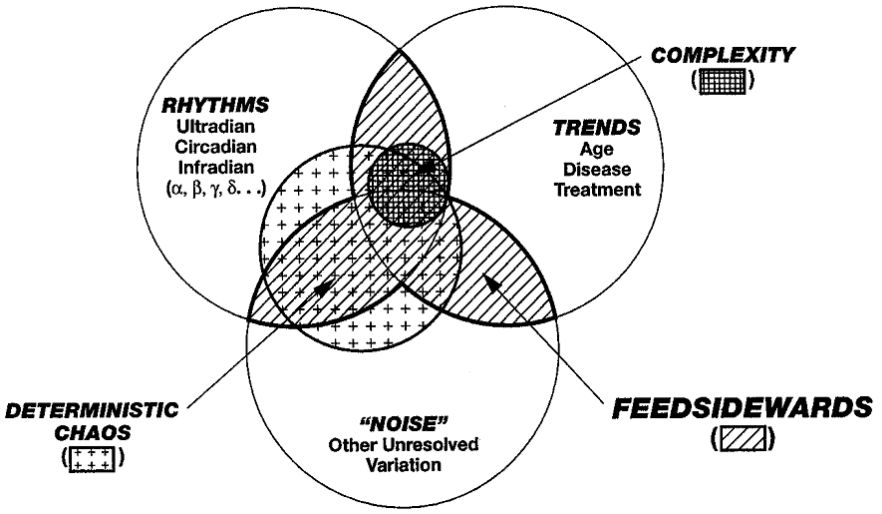


Table 1: Why chronomics -- mapping variability and its mechanisms in and around us

View of:	I. Homeostasis: Response physiology outside the normal range	II. Chronomics: Everyday physiology in the normal range	Utility of II
1. Definition of normalcy, e.g., health	Negative: absence of abnormality, e.g., of signs, symptoms, biochemical abnormality or disease[a]	Positive: by endpoints from parametric and nonparametric assessment of rules in variability and corresponding ranges of acceptability	Time structure is the control in whatever we do, replacing time-unqualified baselines based on spot checks
2. Endpoints	• Original values: casual measurements at times of convenience, not necessarily of pertinence (e.g., of "the" blood pressure with >40% uncertainty in diagnosis in cases of borderline hypertension): time-unspecified: • mean • standard error • day-night rhythms	Endpoints in chronomes[b]: time-coded: • original values • standard deviations (e.g., 6-h, 24-h) • MESOR(s) M • amplitude(s), A • acrophase(s), ϕ • periods, τ • waveform(s) (A, ϕ) • trends • chaotic endpoints • residuals	• Provides information in chronobiologic software for quantifying health • Guides timed treatment that, e.g., has greatly prolonged the survival of cancer patients • Validates treatment effects of harmonics
3. Quantification of normalcy, e.g., health	Population-based: percent abnormality, e.g., morbidity and mortality	Individualized endpoints: P-values for statistical significance and for scientific (e.g., clinical) signification of endpoints of variability	Recognizing risk elevation or other abnormality before overt disease

4.	INTERPRETATION OF REALITY	**HOMEOSTASIS:** NO NEED TO MEASURE MORE THAN SPOTCHECKS. PUTATIVE (IMAGINARY) SET POINTS	**CHRONOMES IN TIME SERIES:** CONSISTING OF a) RHYTHMS, b) TRENDS, c) DETERMINISTIC AND OTHER CHAOS, d) ANY RESIDUALS AND INTERACTIONS AMONG a, b, c AND d	**DETECTING CHRONOME ALTERATIONS:** 1) CIRCADIAN OVERSWINGING OF BLOOD PRESSURE OR 2) DEFICIENT HEART RATE VARIABILITY OR 3) ABOVE-THRESHOLD PULSE PRESSURE 4) ALTERED ABOUT-YEARLY RHYTHMS IN CIRCULATING PROLACTIN AND TSH SIGNALING BREAST AND PROSTATIC CANCER RISK ELEVATION
5.	ATTITUDE TOWARD VARIABILITY	**FOE:** IGNORED OR VIEWED AS A CONFOUNDER	**FRIEND:** OF INTEREST IN ITS OWN RIGHT	AS A TOOL AND SOURCE OF INFORMATION[c]
6.	BIOSYSTEMS' BEHAVIOR IF PERTURBED	SETTLING DOWN TO A STEADY STATE (CONSTANCY) OR LIMITED RANDOM "HUNTING", e.g., AS (MISTAKENLY ANTICIPATED) WHEN A SINGLE BLOOD PRESSURE IS TAKEN AFTER SOME (?30) MINUTES OF REST	**DYNAMIC CHRONOMES THAT** CHARACTERIZE HEALTH WITHIN CHRONOBIOLOGIC LIMITS SET BY THE INTERMODULATION OF THE CHRONOMES' SPONTANEOUS (?)-, REACTIVE (?)-, AND ONE-WAY (?)- OR n-WAY MODULATING (?) RHYTHMS	**POSITIVE INDIVIDUALIZED QUANTIFICATION OF HEALTH**
7.	ANALOGY	**THERMOSTATS** WITH "HUNTING" NOISE	**PENDULUMS** IN RESOLVABLE CHRONOMES	**PREDICTION**
8.	PHYSIOLOGIC OR NORMAL RANGES OF VARIATION	BROAD, INDIVISIBLE; EQUATED TO RANDOM NOISE CURRENT STANDARD FOR DIAGNOSIS AND TREATMENT	STRUCTURED, PREDICTABLE[d]; RESOLVED INTO REFERENCE RANGES (CHRONODESMS) FOR ENDPOINTS OF CHRONOMES	CIRCADIAN BLOOD PRESSURE (BP) AMPLITUDE OR CIRCADIAN STANDARD DEVIATION (SD), e.g., FOR DETECTING EFFECT OF IN UTERO EXPOSURE TO BETAMIMETICS

9.	ACTION?	ELIMINATION OF A CONFOUNDER (RHYTHM): IMPOSSIBLE TO IMPLEMENT; INCOMPATIBLE WITH DETECTION OF CIRCADIAN BLOOD PRESSURE DISORDER COMPATIBLE WITH DIAGNOSING THIS AME PERSON AS NORMOTENSIVE IN THE MORNING AND HYPERTENSIVE IN THE AFTERNOON	MONITORING AND AS-ONE-GOES ANALYSES, AND, ON THIS BASIS, THERAPEUTIC ACTION IF AND ONLY IF AND WHEN NECESSARY	Detects treatable overswinging of bp-a, which carries a 720% increase in risk of ischemic stroke; improves cancer treatment
10.	SOURCES OF VARIATION	EXOGENOUS RESPONSES TO STIMULI FROM PROXIMITY MOSTLY FROM THE HABITAT NICHE	ENDOGENOUS AND EXOGENOUS: RESPONSES TO STIMULI FROM NEAR AND FAR, INCLUDING COSMOS	RESOLUTION OF IMPACT OF STORMS IN SPACE ON MYOCARDIAL INFARCTIONS ON EARTH: NEED FOR A SPACE WEATHER REPORT ?•
11.	MECHANISM	FEEDBACKS ALONG AXES OF TIME-UNQUALIFIED "MODULATION" THAT IS EXPECTED TO ACT AT ANY TIME LIKE THE deus ex machina IN A PHYSIOLOGICAL TRAGEDY SINCE OUTCOMES MAY IN FACT BE UNPREDICTABLE	FEEDSIDEWARDS, TIME-QUALIFIED MANY-WAY INTERNAL AND/OR EXTERNAL INTERACTIONS IN NETWORKS WITH ALTERNATING OUTCOMES WHICH ARE PREDICTABLE (INSOFAR AS THEY RHYTHMICALLY RECUR) AS ACHRONO-MODULATION	PREDICTABLE SINCE RHYTHMIC NEURO-ENDOCRINO-VASCULAR INTERMODULATIONS CAN ACCOUNT FOR OUTCOMES THAT MAY BE AS DIFFERENT AS STIMULATION VS. INHIBITION OF IMMUNITY
12.	HIERARCHY	UP/DOWN	COLLATERAL; ALTERNATING PRIMACY AMONG INTERMODULATING MULTIFREQUENCY RHYTHMS IN CHRONOMES	FOCUSING ON SELECTED TASKS AT DIFFERENT TIMES
13.	TELEONOMY	RIGHTING AND REGULATION	ANTICIPATORY, PREPARATORY COORDINATION	GREATER FLEXIBILITY
14.	SIMPLIFIED ANALOGY	THERMOSTAT	PENDULUM	–

15.	BIOLOGIC EVOLUTION	DARWINIAN, EXTERNALLY ADAPTIVE	MORE AND MORE INTERNAL AND INTEGRATIVE WHILE EXTERNALLY ADAPTIVE TO BOTH NATURE AND NURTURE	INSTRUMENTED SELF-HELP TOWARD A SCIENTIFIC APPROACH TO ETHICS
16.	HEALTH AND ENVIRONMENTAL CARE	MEDICAL TREATMENT OFTEN LIMITED AND LATE, GIVEN MOSTLY AFTER THE DIAGNOSIS OF OVERT DISEASE[e]	OPTIMIZATION ACCORDING TO MARKER CHRONOMES (OF INTERVENTIONS BY DRUGS AND/OR DEVICES, E.G., PACEMAKERS, WITH DIAGNOSIS AND TREATMENT REFINED BY NARROWED REFERENCE RANGE AND ASSESSMENT WITHIN THAT RANGE OF CHRONORISK LEADING TO PREVENTIVE TREATMENT TIMED BY MARKER RHYTHMS (THAT ALSO SERVE TO VALIDATE EFFECT)	E.G., CATASTROPHIC AND IATROGENIC DISEASE PREVENTION
17.	ANIMAL HUSBANDRY, APICULTURE, AQUACULTURE AND ECONOMIC ENTOMOLOGY	CONVENIENCE	CHRONOME-BASED[f]	**OPTIMIZATION:** GREATER EFFICACY; FEWER UNDESIRABLE EFFECTS
18.	VALUE	OFTEN WASTEFUL	COST-EFFECTIVE	WASTE REDUCED
19.	SEEKING INANIMATE AND ANIMATE ORIGINS	STRATIGRAPHY FOR IDENTIFYING, IN GEOLOGICALLY ANALYZED SPACE, SEQUENCES IN TIME; RADIOCARBON DATING	ADDITIONAL TRACING OF CHRONOMO-ONTOGENY AND CHRONOMO-PHYLOGENY[g] IN THE CONTEXT OF GLIMPSES OF CYCLES IN CORRESPONDING SPANS OF A FIGURATIVE COSMO-ONTOGENY	ADDS TO KNOWLEDGE OF THE PAST TO BETTER OPTIMIZE THE FUTURE

20. LIFE IN THE SCHEME OF PHYSICAL AND CULTURAL THINGS	SURVIVAL OF THE FITTEST WITH HUMANS DOMINATING FOOD CHAINS VIEWED IN THE PERSPECTIVE OF BIOENERGETICS IN A MOSTLY TERRESTRIAL ECOLOGY	PHYSICALLY AND SOCIALLY CHRONOMODULATING AND THUS INFORMATIVELY AND INTEGRATIVELY EVOLVING BIOTA MOLDED BY HUMAN CULTURE; homo NOT ONLY faber BUT cosmoinformans AND chronomodulans IN A BUDDING BROAD CHRONOCOSMOECOLOGY[h]	HUMANS SAFEGUARD THE INTEGRITY OF THE BIOSPHERE AS IT EXTENDS INTO THE COSMOS AND AS WE SPECULATIVELY YET BY JOINING THE APPROACHES BY ABLATIONS, SUPERPOSED EPOCHS AND RESONANCE TESTS CONCOMITANTLY EXPLORE THE TEMPORAL ASPECTS OF OUR ORIGINS, POSSIBLY REPRESENTED BY OUR CHRONOMES THAT IN TURN MAY REFLECT A LONG-PAST ENVIRONMENT
21. INVESTIGATOR SATISFACTION	FRUSTRATING WORK WHEN (WITHOUT SPECIFICATION OF CHRONOBIOLOGIC TIMING, EVEN AT THE SAME CLOCK-HOURS) ONE GETS CONFUSING AND/OR OBSCURING, EVEN OPPOSITE RESULTS FROM THE SAME INTERVENTION	SHEER FUN: LONG-STANDING CONTROVERSY IS RESOLVED BY ACCOUNTING FOR BOTH THE GENETIC AND BROADLY ENVIRONMENTAL BASES OF THE FEEDSIDEWARDS AMONG INANIMATE AND ANIMATE CYCLES THAT CONSTITUTE LIFE; DISEASE RISK RECOGNITION PROMISES TO LEAD TO THE PREVENTION OR TIMED TREATMENT OF CATASTROPHIC DISEASES SUCH AS STROKE, CANCER OR SUDDEN DEATH	INCREASED PRODUCTIVITY

Just as contemporary physics, by fission and fusion, gathers more and more energy by splitting the atom, biomedicine gathers more and more information by splitting the normal value range into time structures, thereby resolving, e.g., rhythms (fission) and looking at their feedsideward interrelations (fusion) for a better understanding of an interdigitated, indivisible Janus-faced inseparable soma and psyche.

[a]Health promotion is a step in the right direction, by its recommendations of attention to diet, exercise or relaxation, as long as it is then followed by a chronobiologic assessment of the effect of recommended procedures, rather than merely by the old reliance of ruling out the occurrence of values outside the normal range.

[b]Location and dispersion indices include the determination from histogram of values, of means (arithmetic, geometric, harmonic), median, mode,

minimum, maximum, 100% and 90% ranges, interquartile range, standard deviation, standard error; these endpoints are computed from time-unspecified single values in the context of the homeostatic approach, whereas in the chronobiologic framework the location and dispersion indices are used as such on time-specified samples and on time series-derived parameters, i.e., on each of the endpoints (chrones: M, A, ϕ, [A_n, ϕ_n], etc.) of the chronomes.

[c]An international womb-to-tomb chronome initiative with aims primarily at stroke and other catastrophic vascular disease prevention, by focus, as a start, upon chronocardiology in general and blood pressure and heart rate dynamics in particular. Those interested may consult the chronobiology home page on the Web at http://www.msi.umn.edu/~halberg/

[d]Information from the physiologic range for prevention, diagnosis or treatment is much refined when this range is individualized and interpreted in the light of a personalized background as well as in the context of gender-, age-, ethnicity- and chronome stage-specification.

[e]The need for forecasting storms in space should be explored further on the basis of systematic studies aligning physiological lifetime monitoring and clinical and archival statistical studies with ongoing physical data collection near and far, both for ascertaining effects and in studying countermeasures. Blood pressure, heart rate and other physiological and psychological monitoring would also provide basic information on any cross-spectral and other associations (feedsidewards) within and among biological and environmental chronomes while further providing reference values of medical interest.

[f]Even if some preventive measures have also been long implemented, e.g., by vaccination, and even if recently more and more hygienic measures (such as exercise and caloric, fat and sodium restriction) are also popular, all can be greatly improved by timing designed with chronobiologic individualization. The alternative, current action based on group results, its unquestionable overall merits notwithstanding, fails to recognize, for instance, that the blood pressure response to salt may differ as a function of circadian stage, and there are indeed individuals in whom the addition of salt lowers rather than raises blood pressure.

[g]Even after the death of a cockroach, when bacteria take over, periodicities (e.g., in oxygen consumption) may not be “eliminated”, but continue with increased amplitude. Critical information may be lost by filtering variation deemed to be undesirable since it lies beyond one’s conventional scope.

[h]Development from the egg of rhythms (some may be much older than shards) and of other constituents of chronomes to trace their homeo- or heterochronically roughly “recapitulatory” development across species, with both ontogeny and phylogeny, perhaps tracing in their turn the concomitant development of the geocosmic environment. This distant basic goal can be pursued with the immediate reward of obtaining indispensable reference values for the diagnosis of two chronobiologic risk syndromes, circadian hyperamplitudetension, briefly CHAT, and a deficient heart rate variability, briefly CAHRVs, (an extreme deficit in heart rate jitter). The former is associated with an increase in the risk of ischemic stroke of 715% and the latter with the risk of a myocardial infarction of 550% (Cornélissen et al., 1999, Figure 2).

of ~5 daily measurements of systolic and diastolic blood pressure (Sothern et al., 2005), a signature not only of the Schwabe cycle of relative sunspot numbers (Halberg et al., 2006a and b), of the about 21-year-long cycle of sunspot bipolarity (Hale, 1924) but also of an about 33-year transtridecadal cycle of Brückner (1890), Egeson (1889) and Lockyer (1901), the BEL cycle (Halberg et al., 2009). Thus, we learned that an entity heretofore regarded only as a population cycle is detectable in an individual and anticipate learning about any extrinsic and intrinsic mechanisms pertaining to the didecadal aspects in the physiology of individuals (Sothern et al., 2005; cf. Halberg et al., 2006).

3. Resonant cycles[2] around and in us

As form in space evolved, so did form in time. The claim that nothing in biology can be understood without the idea of evolution, viewed as more or less linear change in form or function (Dobzhansky, 1973; Cairns-Smith, 1982; cf. Darwin, 1859), can gain substance in the light of the underlying more basic findings of a

2 *Cycles, rhythms, periodicities* and *spectra* are not terms found in the indices of books on infant growth and development (Tanner 1981; Roche 1992; Nicoletti et al., 2004, 2006). Indeed, much progress has been made in the study of growth and far beyond this topic, without considering rhythms or broader chronomes. To cite just two examples from the past century, invaluable drugs such as sulfonamides and antibiotics were added to the weapons against infectious diseases (Sutcliffe and Duin 1992), that showed rhythms in their recurrence along the scale of a year (De Rudder 1952). The advance was made without considering these cycles or others such as Alexander Leonidovich Chizhevsky's (1938) demonstration of a circadecadal rhythm in the incidence of cholera in Moscow (Halberg et al., 2001e). As a second precedent, by the middle of the 20th century, cortisone made people lamed by arthritis walk again without the use of information on the very pronounced 24-hour change in circulating, salivary or urinary cortisol. Thus, recognizing the apparent dispensability of periodicity in two major clinical discoveries of the past century, only with due humility do we report, i.a., on a cellular cycle with a sequence of RNA before DNA and thereafter mitosis, of about 24 hours and on didecadal population rhythms in neonatal body dimensions, among others. In so doing, we are doubly cautious since we qualify many of today's studies of growth in which several major ideas that were useful in the past as a starting point for experimental medicine, are here abandoned rather than severely restricted in scope. Table 1 suggests how to overcome homeostasis (Cannon 1932; cf. Halberg 1967). The timing of aspirin administration is not currently considered by the medical profession. But it is documented that aspirin has an effect related to the prophylaxis of heart effects in the morning (an effect that with some endpoints tested decreases as the drug is taken later in the day and is not detected in the evening), while a slight hypertensive effect in the morning becomes antihypertensive in the afternoon (Cornélissen et al., 1991; Hermida et al., 1994; Siegelova et al., 1995). The importance of timing may be less with antibiotics, but the reversal of an effect simply as a function of timing also applies to the effect of an ACTH analogue on DNA labeling (Walker et al., 1985; cf. Cornélissen and Halberg 1994), Figure 1e, Section IID and a difference between "no effect" and a potent effect is found upon circulating cortisol in patients with arthritis (Günther et al., 1980).

host of reciprocal cycles in and around us that evolved through phylogeny and may in part be recapitulated in ontogeny and that constitute the essence of life. More than the circadian rhythm may be coded in genomes (Cornélissen and Halberg, 1994; Halberg et al., 2000a and b, 2003a). Dating via amalgamated rhythms of photic and non-photic origin in phylogeny and ontogeny (Halberg et al., 2004a) may underlie and contribute to both genetics and the evolution of human (and other) physical and intellectual growth and development (Halberg et al., 2004b).

Against this background, the concept of a relative constancy of the internal environment formulated by the aging Claude Bernard (1885) is in stark contrast to the actively somewhat younger Bernard's published realization two decades earlier that one of his two major discoveries was the extreme *variability* of the internal environment (Bernard, 1865; cf. Halberg, 1967). Likewise, a wealth of prior evidence notwithstanding, as Rubin (1984) writes, one may find statements that cell division in the gut proceeds at a continuous rate throughout the 24-hour span (Bertalanffy, 1960; Hagemann, 1976; Nicolini and Baserga, 1976) in keeping with Lajtha et al. (1957), Quastler and Sherman (1959), Lipkin et al., (1961) and Lipkin and Quastler (1962a, b). The assumption that cell proliferation (implied or explicitly stated) occurs randomly was based on spotchecks that can show mitoses in the intestine and in other organs "at any time", a fact compatible with a drastic change from a very few to very many, as had been documented earlier. Cycles consisting of sequences of mitosis, followed by RNA and then DNA formation before the next mitosis, replace the generally accepted dogma that information in an organism flows linearly (rather than cyclically) from DNA $\Rightarrow$ RNA $\Rightarrow$ protein.

Ignorance of cycles can lead to blunders, notably when a phenomenon is influenced by or depends on hormones undergoing multifrequency rhythms (Halberg et al., 2000a). The avoided misinterpretations, published only to indicate likely sources of blunders, led to the recognition of the fact, and thence to the proposition, that much in science, biological or other, should be tested with an account of the essential control information available in the details of the many cycles around and in us. This truism applies equally to scholars in molecular (as in integrative) biology who can all benefit from the need for quantification (Katinas et al., 2005; Ptitsyn et al., 2006; Zvonic et al., 2006). These cycles, and the broader time structures of which they are just a part, remain to be mapped in any experimental approach that involves sampling as a function of time. Cycle assessment replaces spotchecks of phenomena, such as mitosis, that need to be mapped by time series, no longer by marker rhythm-guided 2-timepoint explorations (that remain of historical interest). In retrospect, the two-timepoint approach is best replaced by distributing the units (e.g., experimental animals) sampled more or less equidistantly along the period of an anticipated cycle, rather than at a known peak and trough.

Analyzing data obtained in Minnesota by ourselves and/or with Marmion W. Houglum, Hans Mühlemann, Jens Waerhaug, Helmut A. Zander, and, in particular, the late Anand P. Chaudhry (Halberg et al., 1954; Zander et al., 1954; Chaudhry et al., 1956a-c) and those from the school of John Pauly and Robert E. Burns in Arkansas, due mainly to the late Lawrence E.

Scheving (Scheving, 1959; Scheving and Chiakulas, 1961; Halberg et al., 1978; Scheving et al., 1983), by Leopoldo Garcia Alonso et al., (1993, 1998) and the late Boris A. Nikityuk, a few multifrequency aspects of the time structure of growth emerge. We separate what the naked eye can see in time series -- time-m**a**croscopy -- from time-m**i**croscopy, with focus by inferential statistical methods upon diversity not only in space (e.g., genetics) but above all in a complementary chronobiology, the study of mechanisms underlying biological temporal diversity.

4. Cell division is not "homeostatic"

A 24-hour periodicity of mitotic activity in laboratory animals and humans as an example of a biological rhythm in a fundamental cell mechanism was found relatively early with light-microscopy. This periodicity is physiological, even though workers in morphology and pathology who, with notable exceptions, have not sought to identify the physiological mechanisms of the phenomena they were investigating, have recorded the abundant data on which the early observations of a periodicity can be based.

After the earlier demonstration of 24-hour periodicity in mitotic activity in plants (Kellicott, 1904; cf. Karsten, 1918), Fortuyn-van Leyden (1917) was apparently the first to present evidence of periodicity in the mitotic activity of a mammalian tissue, noting that the number of mitoses in the mesentery, in the corneal epithelium and in the crypts of Lieberkühn of two-day-old kittens increased in the evening and early morning and declined in the late morning and early afternoon. In 1924 she found for the materials from her first study that the same pattern of activity held in the spleen, lymph nodes, thymus and bone marrow. Another publication of Fortuyn-van Leyden (1926) reported that the mitotic rate in the crypts of Lieberkühn in two-week-old mice was maximal in the late morning and steadily decreased to reach a minimum in mid-afternoon.

Several years later, Ortiz Picon (1933) investigated the effects of aging on the mitotic rate in the epidermis of mice. He noted a decrease in the number of mitoses during the evening and early night hours to about one-third of the noon value, and found this decrease to be greater than the decrease in the average number of mitoses with age. Ortiz Picon's very limited data, obtained however on littermate animals of the same sex, fed the same diet and kept under comparable conditions, are summarized under the heading "Something about time of day and cell division" and are "meant to demonstrate the existence of an influence of the time of day upon cell division in the epidermis solely in order to forestall possible mistakes in interpretation of data regarding mitotic rates at different chronological ages." Ortiz Picon was first to consider and compare two parts of two elements of the growth chronome, the trend with age and a rhythm, but as yet only from the viewpoint of a potentially confusing source of variation and only as a feature of an unspecified time of day.

His conclusion illustrates the attitudes toward phenomena with 24-hour periodicity exhibited by investigators, who regard rhythms merely as a source of variability in experimental data. In fairness to Ortiz Picon, however, it should be mentioned that he alludes to the possibility that periodically secreted hormones could bring about a periodicity in mitoses. He thus hints at the broader importance of the phenomenon and at its endocrine mechanisms.

A year later, Carleton (1934) reported a maximum around midnight and a minimum around noon for the numbers of epidermal mitoses in 8 to 168 hour-old male mice, kept under routine circumstances of illumination. The same investigation found 1. a periodicity in mitotic activity of mice kept in darkness from the 23rd to the 37th day post partum and 2. a loss of periodicity in the mitotic activity of a small series of immature animals, exposed continuously to artificial light, findings now qualified by the persistence of statistically significant within-day differences in both continuous light and continuous darkness (Halberg and Barnum, 1961).

A thorough demonstration of periodic activity in the epidermis of the albino rat is given by Blumenfeld (1939), who also points out that evaluation and/or comparison of data obtained in investigations on periodicity is feasible only under controlled circumstances. He was apparently the first investigator who endeavored to control the age, the species and the number of animals in a sample as well as the external conditions of the experiment (Blumenfeld, 1944). In skin from one-month-old rats, kept under normal conditions of illumination, he found four times as many mitoses at 08:00 as at 20:00. Blumenfeld suggests that the factors which coordinate mitosis vary inversely with the function of an organ. Mitotic activity in the renal cortex is found to be minimal at the time of maximal urinary excretion and maximal at the time of minimal urinary excretion (Blumenfeld, 1938). A similar inverse relationship is found between the rate of mitotic activity in the submaxillary gland and that of functional activity, which is associated with food intake (Blumenfeld, 1942). Blumenfeld divides the basic processes of a cell into functional and vegetative activities: one state ceases when the other begins. Cells undergo division during the vegetative state, upon cessation of the functional state. This concept was formulated earlier by Politzer (1928), who found that moving cells do not divide, and by Peter (1929), who found that increased activity in the tubular epithelium of the renal cortex inhibits mitosis and that decreased activity stimulates it. Blumenfeld concluded that a mechanism of periodicity in cell division must reside within an organ itself. This important finding is not at variance with later work that demonstrates for several tissues a relationship between the periodicity in mitotic division and the periodicity in the activity of an organism as a whole. This observation suggests an added, rather than an alternative mechanism of integration of 24-hour periodicities, including mitotic periodicity, at the organismic level, rather than exclusively at the organ level.

Bullough (1948a,b; 1949a,b) determined the 24-hour rhythm in spontaneous bodily activity of 3- to 4-month-old male mice simultaneously with the 24-hour

rhythm in mitosis of the skin and various other organs. He noted a 24-hour periodicity in the average number of mitoses in the epidermis, the esophageal and duodenal mucosa, and the epididymis, which showed an inverse relationship to bodily activity. A minimum in mitotic activity was found during the waking hours and a maximum during resting. The fall in mitotic rate, which was observed in controls subsequent to the evening increase in bodily activity, was delayed when, by means of a hypnotic, some animals were induced to sleep beyond this time. Conversely, by forced exercise, mitotic activity was kept at a low level. Furthermore, it was noted in this latter study that the mitotic rate in animals forced to exercise fell below any previously noted minimum, and remained depressed after the animals had been removed from the activity cage and allowed to nap for 2.5 hours. "The outcome of the revolving box experiments seems to indicate that excessive exercise or a heightened metabolic rate results either in the production of a mitosis depressing substance which takes some hours to be eliminated, or in the using up of some mitosis stimulating substance which takes some hours to reform in sufficient quantity" (Bullough, 1948a and b, 1949a and b).

Further studies by Bullough (1949b) revealed an inverse relationship between the 24-hour periodicity in blood sugar, described for the rat earlier by Pitts (1943), and the periodicity of mitotic activity. During sleep, the blood sugar decreased while the mitotic rate increased.

Cooper (1939) was apparently the first to report periodicity in mitotic activity of human epidermis (see also Fisher, 1968). She examined the prepuces of 57 neonates and noted an increase in the average number of mitoses in the late afternoon and early evening, with a subsequent decrease in the later part of the night, which ends in a lower average number of mitoses in the morning. Plotting mitosis against time of day, there is a suggestion of minor maxima and minima within the 24-hour periodicity. Studies on a smaller number of prepuces by Broders and Dublin (1939) confirm Cooper's results.

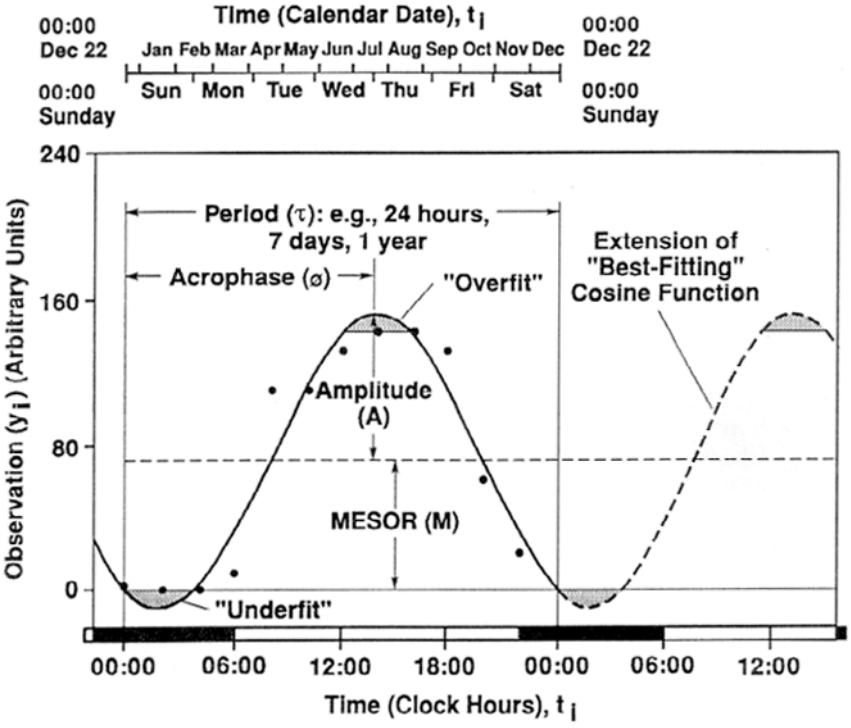
An absence of 24-hour periodicity in mitotic activity of a malignant tissue was reported by Dublin, Gregg, and Broders (1940) in specimens from five cancers of the large bowel. This finding was extended by Blumenfeld's (1943a) experiments to induced epidermoid carcinoma in the epidermis of male mice. The cells of the tumor were found to divide at a uniformly high rate: the mitotic activity of the malignant tissue was comparable to that seen in the epidermis of non-tumorous controls when the rhythm of the latter was at its peak. This finding gains in importance from the demonstration of the same author that in contrast to malignant tissue, the regenerating epithelium of the rabbit had a higher mitotic rate than the rate of controls, yet still exhibited periodicity (Blumenfeld, 1943b). It is thus apparent that in a first descriptive stage of our knowledge on mitosis, a 24-hour periodicity in the average number of mitoses has been ascertained for a variety of tissues, in different species and at different chronological ages. The 24-hour periodicity has been reported to be synchronized with the activity, as well as with the feeding habits

(Blumenthal, 1950) of the animal. It has been reported to persist for at least two days in a "constant" environment, and it is modified under various experimental circumstances. It is different at different chronological ages. It is seen in rapidly growing epithelium, but was not found in malignant tissue.

The data reviewed by Halberg in 1953 were compatible with the assumption of a physiological 24-hour rhythm in mitotic activity, which is altered or obliterated under certain experimental or pathological circumstances. As in most other fields of biological 24-hour periodicity, the factors with which the rhythm is synchronized as well as the hormonal mechanisms which bring about the rhythm were then subjected to subsequent investigation. The periodicity of mitoses was found to persist in continuous darkness and in continuous light, as subsequently documented (Halberg and Barnum, 1961).

For the purposes of setting the stage for a new science, circadian rhythms are characterized by a period of about 24 hours, a MESOR or rhythm-adjusted mean; double amplitude, a measure of the extent of predictable change without a cycle; and the acrophase, a measure of the timing of overall high values occurring in each cycle, Figures 3. The MESOR is usually more accurate and more precise than the arithmetic mean, Figure 4. The whole of 24-hour rhythms, including a rhythm in mitotic activity, was conceived as a series of cyclic physiological processes, integrated into a physiological sequence with differences in phase coordinated at both the cellular, organ, organism and species levels by a set of physiological mechanisms, prominently involving the adrenal cortex and the broader adreno-hypophyseal-hypothalamic-pineal network, Figure 2 (Halberg, 1953; Halberg et al., 2003a, Scheme 1). Bullough (1948a and b, 1949a and b) noted that adrenal medullary hormones depress mitotic counts. In our hands, studies on the pinnal epidermis of mice (Chaudhry et al., 1956a; cf. Chaudhry et al., 1956b; see also Chaudhry et al., 1956c) in retrospect are qualified by a meta-analysis of the effects of epinephrine in larval urodele tissue carried out by testing any effects upon mitosis around the clock with widely differing results (Chiakulas and Scheving, 1964, 1965; Chiakulas et al., 1966). Figure 5 suggests a sinusoidal circadian stage-dependence of the response of cell division to epinephrine in controls with saline are ignored. Figure 6, based on a comparison with saline-injected controls, shows in the same tissue at one test time a statistically significant increase in cell division. Melatonin, also credited with antiproliferative activity (Cos et al., 1996; Sainz et al., 1998; Chen and Chen, 2001; d'Istria et al., 2003), can have opposite effects upon malignant growth in a predictably stage-dependent way and are outstanding (Cornélissen et al., and Halberg et al., in Bartsch and Bartsch, 2001). The demonstration of the results in figures required a special methodology of curve-fitting, complementing and, for parameter estimation, replacing the stacking and other non-parametric procedures used earlier.

Figure 3 - Estimations of parameters M, A and Ø by least squares fit of cosine model with fixed period*.



* $y_i = M + A\cos(\omega t_i + ø) + e_i$; where $\omega = {}^{2\pi}/_{\tau}$, t_i = time; y_i = observation at t_i and e_i = error at t_i; assumed as a first approximation to have the same independent normal distribution with mean zero and unknown variance σ^2, regardless of time; F statistic from zero-amplitude test compares sum of squares (SS) accounted for by fitted model either with the residual SS (original or pooled cosinor) or with the SS due to pure error, uncontaminated by lack of fit (unpooled cosinor).

Figure 4 - Advantages of the mesor over the arithmetic mean in estimating location.
The MESOR has smaller bias in the case of unequidistant data. Its standard error (SE) reflects the variability of the data after the variability accounted for by the rhythmic pattern has been removed. It differs from the global SE reporting the total variability of the data (most of which can be ascribed to the rhythmic structure). © Halberg.

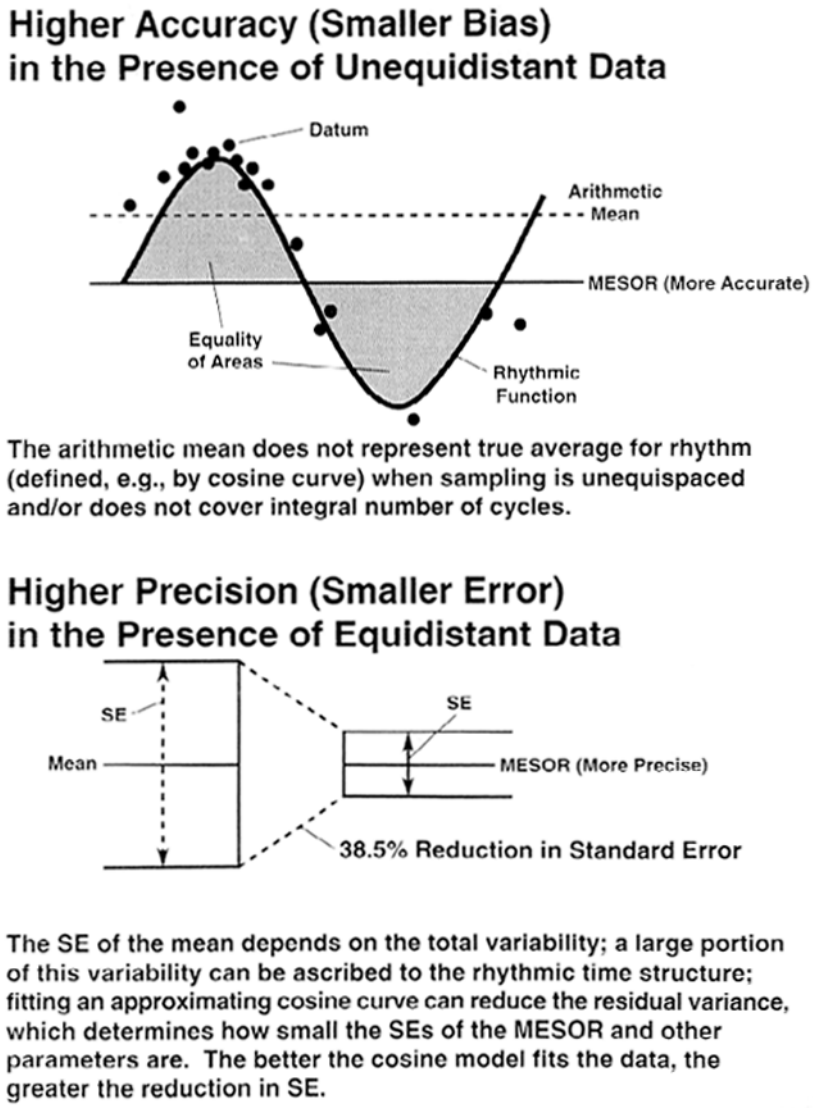
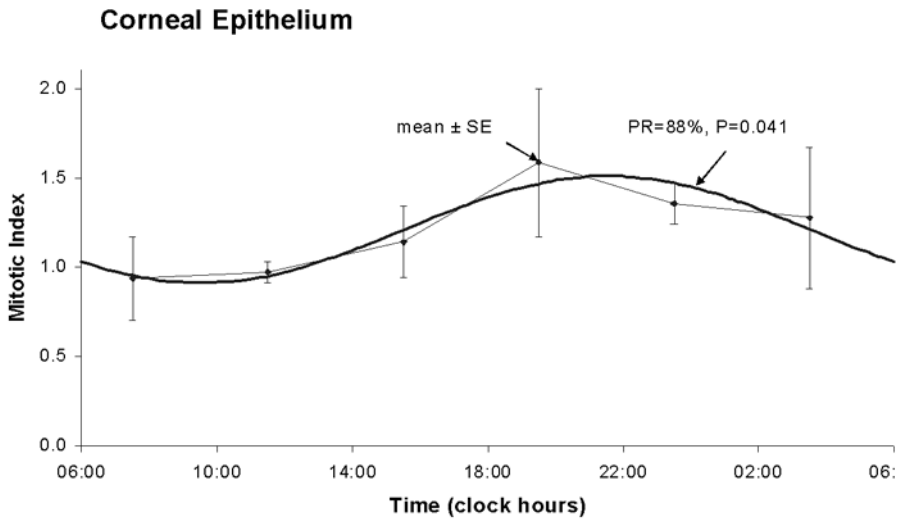
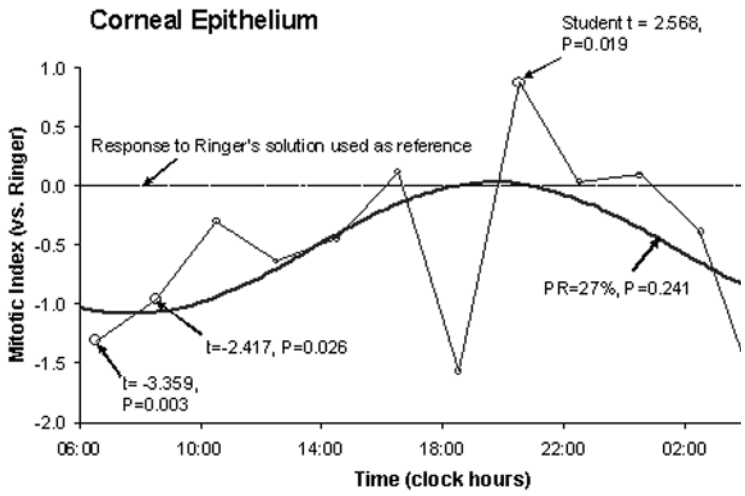


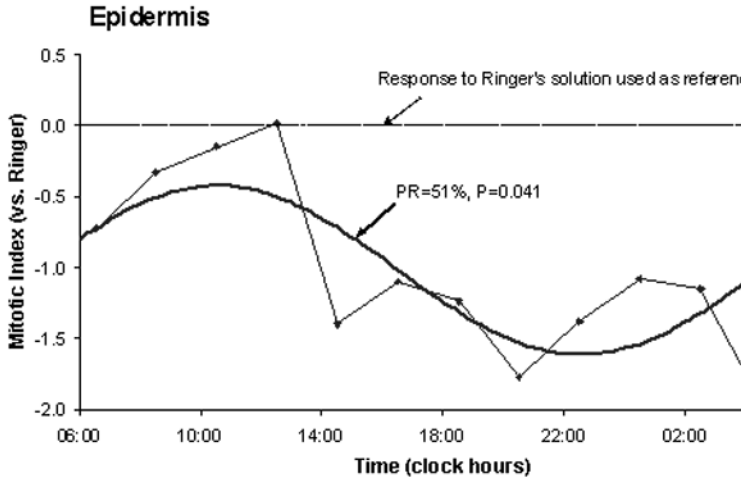
Figure 5 - Circadian stage-dependent effect of exogenus epinephrine on mitotic index of corneal epithelium in larval urodele tissues



(Meta-analyzed data from Chiakulas JJ, Scheving L E, Winston S, Experipental Cell research 1966; 41: 197-205)

Figure 6 - Meta-analysis of changing mitotic response to epinephrine*





* Original data on urodele larvae (of *Taricha torosa*, 10 per timepoint in LD12:12) of Chiakulas JJ, Scheving LE, Winston S. The effects of exogenous epinephrine and environmental stress stimuli on the mitotic rates of larval urodele tissues. Experimental Cell Research 1966; 41: 197-205. Analyses of differences between 0.01 ml of 0.5% epinephrine and 0.01 ml Ringer's solution (reference; dashed horizontal lines), injected intraperitoneally. Larger circles (top) indicate statistically significant difference by Student t-test.
PR: Percentage Rhythm (proportion of variance accounted for by fitted curve).
P: corresponding P-value from zero-amplitude (no-rhythm) test.

5. Methods for analysis

Standards such as the length of the king's arm were eventually replaced by increasingly precise, generally and consistently applicable comparable measures. The same desideratum becomes a sine qua non in dealing with cycles. To agree on what is and what is not a cycle, hypothesis testing, e.g., the rejection of the assumption of the zero-amplitude, can be used. While most people will agree that an arm is an arm, this does not apply to the cycle in core temperature after ablation of the suprachiasmatic nuclei (Halberg 1983) when opinions can differ simply because hypothesis testing by cosinor is or is not used (Refinetti et al., 2007). It is indispensable to objectively assess the length of each cycle, i.e., its period, t, and the extent and timing of change, the amplitude, A, and acrophase, ϕ, by a fundamental cosine fitted or by a special model in special cases. This first set of generally applicable measures (Fig. 3), is best obtained, each with an uncertainty such as a 95% confidence interval (CI). The waveform is then taken into account by the magnitude and orthophase, defined by the (A, ϕ) of all statistically significant harmonics, added each with its uncertainties. The use of these universally applicable endpoints yields as a dividend, Figure 4, an improved **m**idline-**e**stimating **s**tatistic **o**f **r**hythm, the MESOR, which is usually more accurate and more precise than the arithmetic mean and is obtained from a parametric cosine fitting, called the cosinor, and from a set of other procedures noted in Table 2 and is complemented by a non-parametric stacking in a plexogram. Both approaches, the parametric and non-parametric, are applicable to individuals and to populations; both are inferential statistical rather than only descriptive in nature. Both approaches need norms. Such norms remain to be established for healthy growth in longitudinal studies that may focus and can resolve more than one spectral component, as shown for a test series in Table 2.

Inferential statistical approaches (Albert, 1999; Hawkins, 1829) to rhythms early in the second half of the 20th century had relied on phase only, without considering the amplitude in attempting to quantify rhythms. The time-macroscopy of activity onsets still relies often only on phase today, and the estimation of the uncertainties in the estimation of phase was an important step by the late Ed Batschelet (1965). We complemented his time-microscopic approach as soon as we could with the inclusion of a test of the amplitude in the validation of an anticipated rhythm by the cosinor method (Halberg et al., 1967). Eventually, Batschelet did write, as he put it verbatim, that while he was not yet ready to sanctify the original single cosinor, he did beatify it (Halberg et al., 2003a). A genetic anchor was thus documented for the circadian amplitude of human heart rate based on a study on twins reared apart (Hanson et al., 1984). The Minnesota psychologists Thomas J. Bouchard and David T. Lykken, with psychiatrist Elke Eckert and cardiologist Naip Tuna, recruited twins reared apart from birth, some of whom met for the first time in Minnesota. A comparison of electrocardiograms from dozens of pairs of mono- vs. dizygotic twins showed the emergenic heritability of the adult human heart rate's extent of change along the 24-hour scale

Table 2 - Comparison of methods applied to noisy test series with two components with close periods. Only two approaches (7 and 8) resolve both components.

$Y_i = 100 + 10 \cos(2\pi t/24 - \pi) + 2 \cos(2\pi t/24.8 - \pi) + 5\,R$, where i = 1, …, 336 ($\Delta t$=1 hour; T=14 days) and R is uniformly distributed with zero mean and range =1 (±0.5)

N	Method Kind	Period (h)#	MESOR	Amplitude	Acrophase (degrees)	Detection Test	P	N of components detected
1#	"Cosinor"-SC[1]	24.00	100.18	10.47	-98	F(2,333) = 2951.51	<0.001	1
2#	Cosine_fit	24.00	100.18	11.53	-98	GoodFit¶ = 0.001	<0.001	1
3*	Fourier	23.93					<0.001	1
4*	Lomb-Scargle	24.00				Robustness = 96%	<0.001	1
5*	Enright	24.00				Robustness = 96%	<0.001	1
6	ARIMA.MLE in SPLUS§	24.00	100.15 (99.8, 100.5)	10.45 (10.11, 10.80)	-96.5 (-94.5, -101)		<0.001	>1[2]
7a	Linear step 1 (L)[3]	24.00	100.18 (99.98, 100.37)	10.47 (10.20, 10.74)	-98 (-97, -100)	PR=95%	<0.001	
7b	Nonlinear step 2 (NL)	23.97 (23.83, 24.10) 24.63 (24.04, 25.21)	100.13 (99.83, 100.43)	9.75 (7.67, 11.84) 2.49 (0.34, 4.63)	-91 (-78, -105) -98 (-47, -149)		<0.05@ <0.05@	 2
8	Simulated Annealing (GOSA software www.bio-log.biz)	23.96 (23.89, 24.03) 24.6 (24.3, 24.9)	100.4 (100.1, 100.7)	9.6 (8.4, 10.8) 2.5 (1.3, 3.7)	-94 (-83, -105) -94 (-60, -128)		<0.05 <0.05	 2

Acrophase expressed in (negative) degrees, with 360°≡period length, and 0° set to 00:00 at start of series.

Period is anticipated trial period.

* Only one peak detected.

¶ GoodFit: Goodness of Fit.

@ From non-overlap of zero-amplitude by 95% Confidence Interval (CI).

[1]SC: South Carolina: cosinor restricted to 24-hour component, by contrast to Minnesota's cosinor, which includes least squares fit of multiple components consisting of cosine functions with anticipated components not necessarily equal to 24 hours, originally called 'single cosinor' to indicate analyses of individual time series (and NOT of a single component fit), soon thereafter extended to include the chronobiologic serial section and the combined linear-nonlinear rhythmometry, among others; all procedures involving the least squares fit of cosine curves often displayed vectorially along polar coordinates and checked against chronograms and data stacked for the period(s) found, i.e., as plexograms, for each cosinor-isolated component (periods are estimated with their respective confidence intervals).

[2] Structure of residuals found to be correlated and modeled with an ARMA (1,1) model, with AR coefficient = 0.78 (0.49, 0.89) and MA coefficient = 0.54 (0.23, 0.75). Results reported at fixed anticipated period of 24 hours.

[3]Least squares spectrum detects peak at anticipated period of 24 hours and small sidelobes with periods of 26.7 and 21.8 hours resolved nonlinearly as presence of second component with period slightly longer than 24 hours.

6, 7 and 8: 95% CIs in parentheses; 7a and 7b are part of the more extensive, as need be, MN-cosinor.

§Chatfield C. The analysis of time series: an introduction. London: Chapman and Hall; 1984.

(Hanson et al., 1984). The textbook lesson that the heart may continue beating (with its own built-in frequency of ~1 Hz) after the sympathetic and vagal fibers are severed was extended to circadians, with the qualification that organisms are systems open to their environmental magnetic and other fields, and while the beating may persist *ex vivo*, the continued influence of environmental factors has not been ruled out (Halberg et al., 2000b, 2001a). Indeed, the frequency of some geomagnetic pulsations can be in the region of 1 Hz, a point made without implications that similar periodicities are more than hints of primarily evolutionary causal relations. Causality, in some cases, can be supported, however, by remove-and-replace approaches and for the driving of about 7-day (Cornélissen et al., 1996) and 1.3-year cycles (Halberg et al., 2006a and b) in the circulation by solar activity.

With the amplitude assessed as differing from zero (by a CI [95% confidence interval] not-overlapping zero), rhythms could be defined time-macroscopically as recurring physiological changes formulated algorithmically and validated by inferential statistical means (Halberg, 1969, 1980, 1983). More than one "time-microscopically" thus-defined rhythm was found to constitute a periodic component of the spectrum of a biological time series as it lengthens. By the use of a mathematical approximating function such as a cosine curve, endpoint and confidence interval estimates of each spectral component were obtained as rhythm parameters, namely a period, τ, and acrophase, ϕ, and an amplitude, A, and (A, ϕ) pairs of harmonics to determine the waveform, along with a common **m**idline-**e**stimating **s**tatistic **o**f **r**hythm, MESOR (M), are obtained. Figures 3 - 4 compares methods used for the all-important computation of CI, notably of the period of some infradian components, that gain particular importance if we look for reciprocal periods in auxology and around us (Halberg, 1980; Czaplicki et al., 2006; Halberg et al., 2006a and b). Figures 7-11 show the approximation by a single cosine curve of data on pituitary somatotropic hormone, STH, (GH).

As the length of the time series increases and additional components are detected in and around us and as they interact in the organism as an open system, there is an increasingly greater need for relying on parametric and non-parametric methods, but the latter cannot be a substitute for the amplitude derived from the fit of a cosine curve or of several such components and, when need be, of polynomials, to describe trends, often due to an incompletely sampled component with a lower frequency. The τs, As, ϕs and waveforms determined according to classical procedures in physics are recommended for collecting primary reference data bases for rhythm characteristics.

Procedures for comparing relations at several frequencies among 2 or more time series, complement parameter comparisons at a fixed frequency (Bingham et al., 1982). While the latter parameter tests remain useful in circadian physiology at a fixed frequency, time-varying coherences and time-varying phase synchronizations (Halberg et al., 2003c) at many other frequencies as well as at the circadian will also have to be applied. About 24-hour rhythms may disappear as a statistically significant entity in the case of circulating endothelin (Artigou et al., 1993; Tarquini B. et al., 1997a and b).

Figure 7 - Circadian rhythms of clinically healthy adolescents. Growth Hormone, as ACTH, cortisol and glucose in serum, is circadian periodic, as assessed in 6 male and 7 female high school students, 13-17 years of age. Adapted from Lakatua et al. (1974).

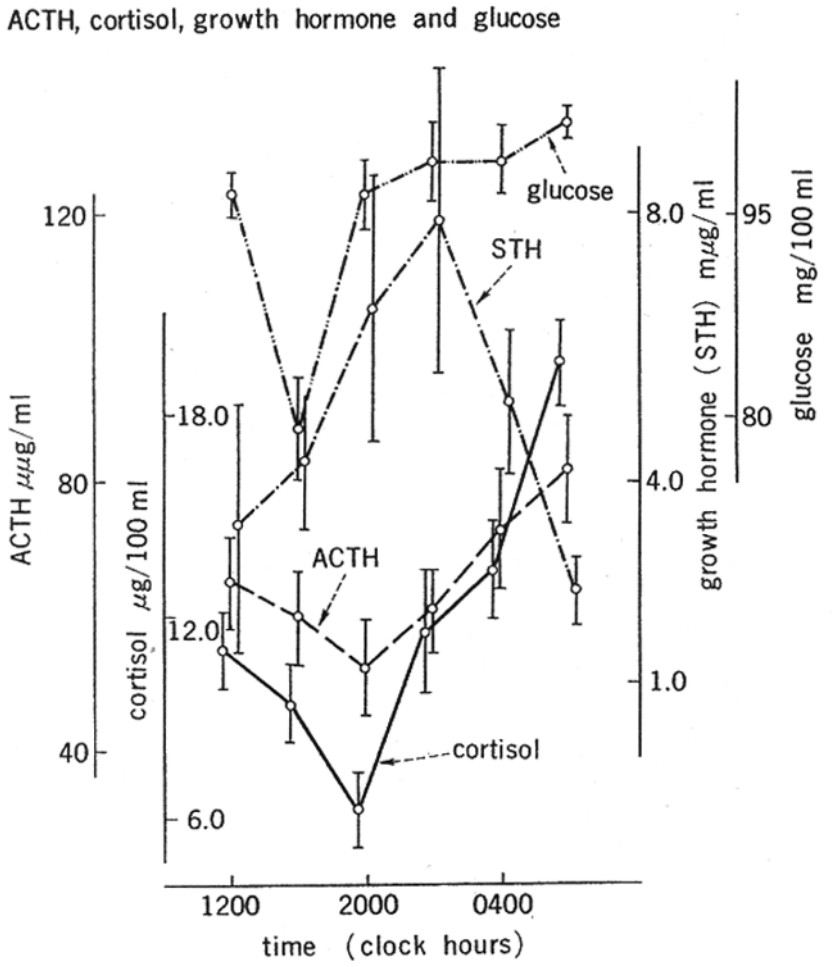


Figure 8 - Circadian rhythms of growth hormone in serum of clinically healthy adolescents. Large amplitude circadian rhythm of serum growth hormone in clinically healthy adolescents, peaking during the rest span. © Halberg.

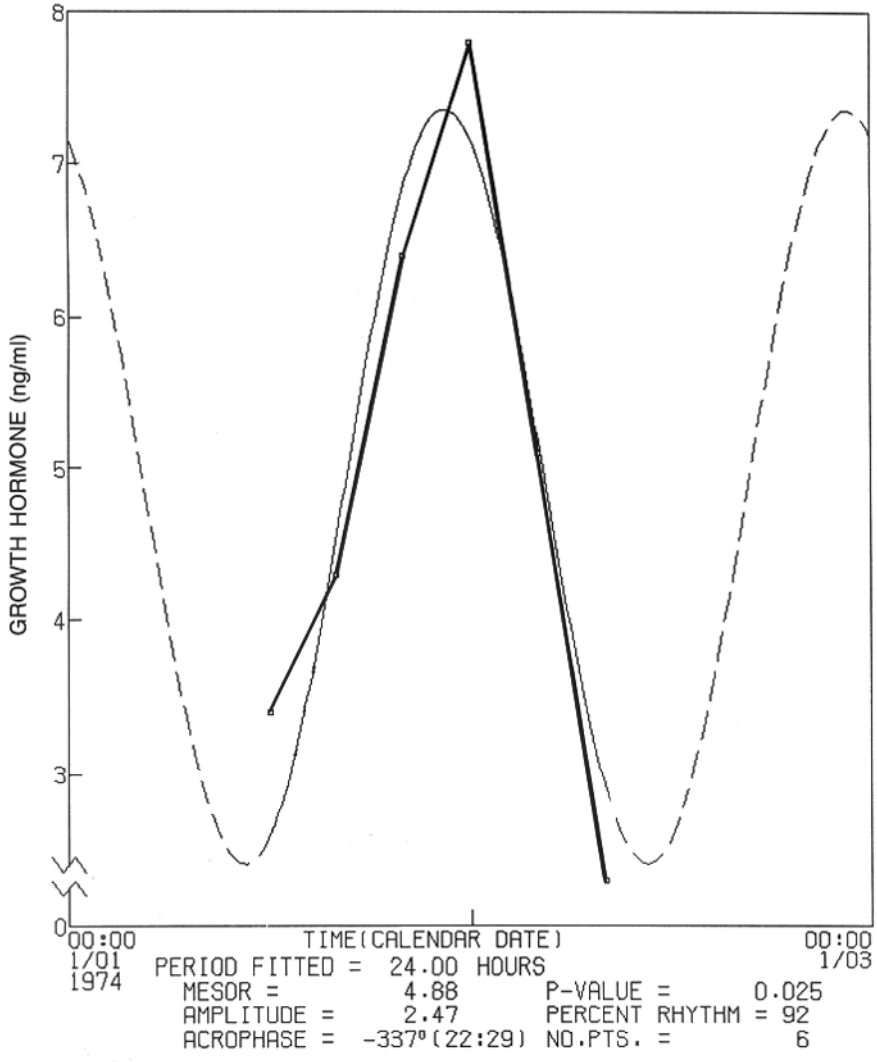
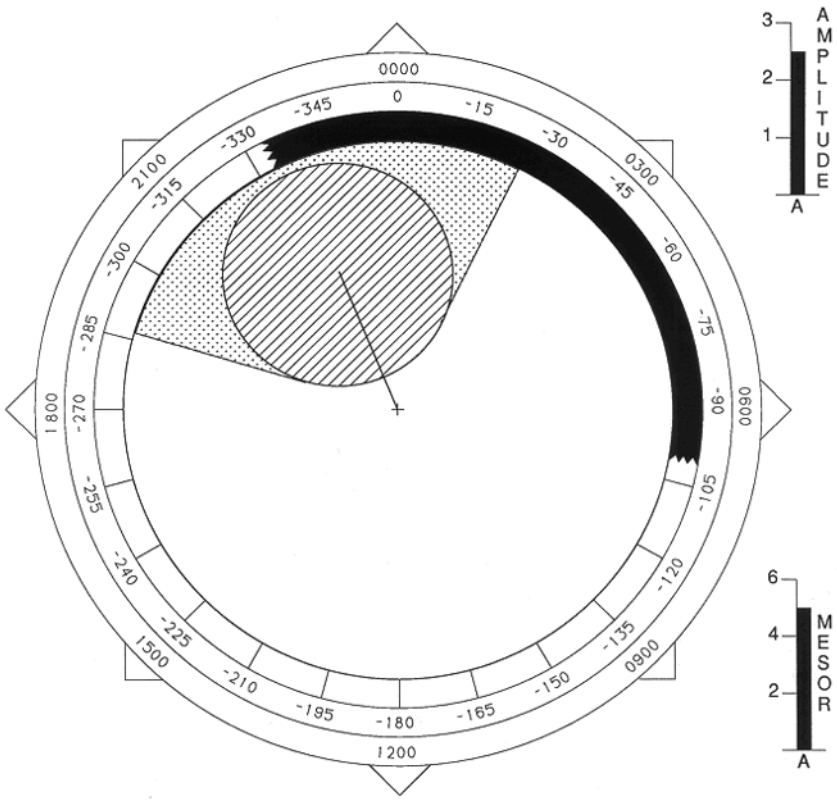


Figure 9 - Circadian rhythms of growth hormone in healthy adolescents, 1974. Single Cosinor Analysis. Cosinor (polar) plot summarizing circadian variation in growth hormone of clinically healthy adolescents. © Halberg.



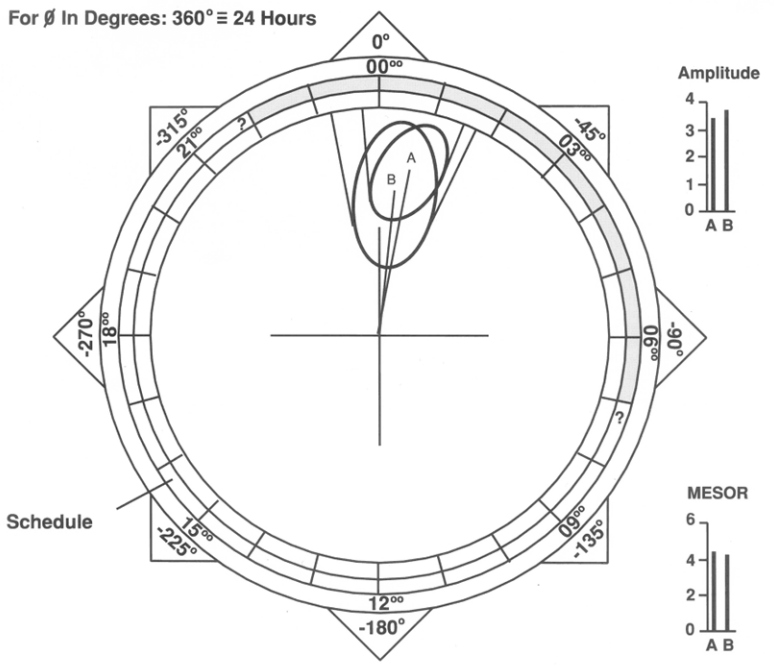
For 0 in Degrees: 360° ≡ 24 Hours

Key	P	N	PR	MESOR +-SE	AMPLITUDE *	ACROPHASE (Ø) *
A SERUM GH	.025	6	92	4.88 .31	2.47 (.57 4.38)	-337° (-287 -28)

P = PROBABILITY OF HYPOTHESIS: AMPLITUDE = 0; N = NUMBER OF OBSERVATIONS
PR = PERCENT RHYTHM (PERCENTAGE OF VARIABILITY ACCOUNTED FOR BY COSINE CURVE)
*CONSERVATIVE 95% CONFIDENCE LIMITS (PARENTHESES) DERIVED FROM COSINOR ELLIPSE
CHRONOBIOLOGY LABORATORIES – UNIVERSITY OF MINNESOTA – MINNEAPOLIS, MN 55455 (612) 624-6976

5/89
GA 5.2

Figure 10 - Rhythmic changes of growth hormone (ng/dl) in boys and girls (Spain). Reproducibility of the circadian variation in circulating growth hormone in children, assessed separately in boys and girls. Note acrophase during the rest span. Data from L. Garcia. © Halberg.



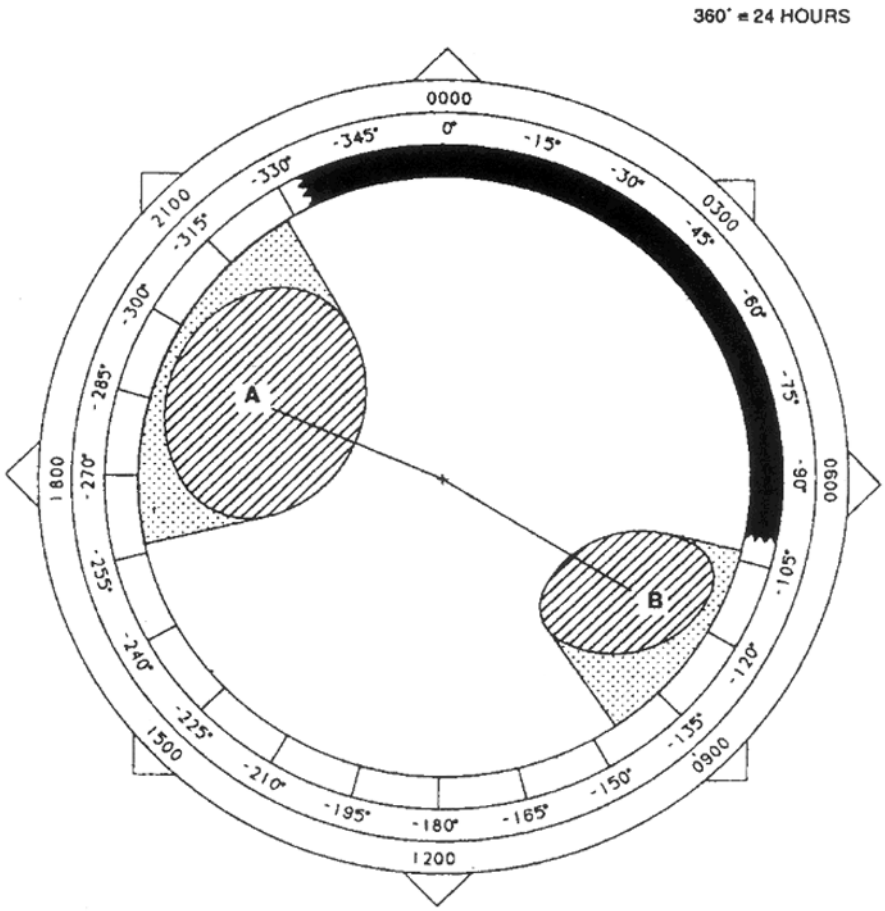
Population-Mean Cosinor

Key	P	N	PR	MESOR ± SE	Amplitude*	Acrophase (ø) *
A Boys	< .001	98	32	4.32 .35	3.6 (2.53 4.72)	-11°(-357 -22)
B Girls	< .001	46	34	4.24 .62	3.9 (1.83 5.96)	-6°(-348 -25)

P = Probability of Hypothesis: Amplitude = 0; N = Number of Series Used by the Mean Cosinor Technique To Find Ellipse

* Conservative 95% Confidence Limits (Parentheses) Derived From Cosinor Ellipse

Figure 11 - Cosinor analyses of a pool of all values obtained in studies on 6 h day (during rest and also during activity) by Dr. Helen Morris. See text. Importance of a built-in circadian component in circulating growth hormone. Data collected from four small children on a 6-hour day for 48 hours. GH has an acrophase of -293° almost in antiphase with that of cortisol. Data from H. Morris.



6. Circulating growth hormone

Data displayed time-macroscopically as averages in Figure 7 stem from 6 boys and 7 girls, median age 15.3 yr (range 13 to 17), who spent a 30-h span in 1971 at St. Paul-Ramsey Medical Center (St. Paul, Minnesota), in a study by Erhard Haus, summarized with him elsewhere (Halberg et al., 1989). The naked eye sees a circadian change in serum concentration of GH (on graph STH for somatotropic hormone), but time-microscopic studies are needed to quantify some reproducible aspects of the variation, e.g., by the fit of a 24-h cosine curve, Figure 8. Such a fit allows rejection (P=0.025) of the no-rhythm assumption, i.e., of the assumption of a zero circadian amplitude. Around a MESOR of 4.88 ng/ml, there is a change with a double amplitude of 4.94 ng/ml and an acrophase at 22:29 hr:min after local midnight, or at -337° (with 360° º 24 h), Figure 9. Daily emphasis on metabolism for growth and repair alternate with energy metabolism defraying the cost of motor and other activity. The phase comparator of the underlying networking mechanisms is in part in the pituitary and shifts from emphasis on GH to ACTH production and vice versa (Halberg, 1953). As predicted (Halberg, 1953; cf. Halberg et al., 1959), the phases of GH and of ACTH are drastically different. The ACTH acrophase (Lakatua et al., 1974) is at -108°, i.e., 131° distant from the acrophase of GH (at -337°). The circadian cosinor results have been checked in several studies, with growth below vs. within socially accepted limits: similar MESORs, Figure 10, and even larger amplitudes than those in Figure 9 were found (Hermida et al., 1988, 1989).

The importance of a built-in circadian component in circulating GH is apparent from analyses of a study carried out by Dr. Helen Morris, who studied four small children, ages 4-8 yr, in clinical health and asthmatic children, 5 boys and 5 girls, 9-15 yr of age. Each study covered 48h and was preceded by 16-18 h during which the 24h routine was replaced by a "6-h day". 8 consecutive spans, each of 6 h, each involved an average of 2.5 h spent in sleep and/ or rest, and exercise and meals every 6 h. In one study, blood samples were taken prior to eating, after the children had been awake and engaged in quiet activity for 2 h. In another study, blood was sampled as children were awakened individually from 2 h of sleep. The first study began at 08.00 or at 14.00, the second at 02.00. The blood sampling interval in each study was of 6 h and this sampling covered 48 h. In the pooled results from 29 series, a circadian rhythm is demonstrated below the .001 level, for both GH and cortisol. The GH acrophase is at -293°, with a 95% confidence interval extending from -257° to -328°, Figure 11. The cortisol acrophase is near antiphase with the 95% confidence interval extending far removed from that for GH. A large difference in phase is demonstrated between GH and, in this case, cortisol rather than ACTH; the latter hormone is anticipated to peak nearly in phase with cortisol.

A single cosine curve poorly approximates the sometimes irregular variation in circulating hormones, including the GH concentration in the blood of a given densely sampled individual. More complex models are used when denser data become

available. A linear least-squares spectral analysis has revealed components of 24, 16 and 12 h for boys, girls and all subjects in a study of 32 children of both genders, 6-14 yr of age, of short stature in the light of local standards (Hermida et al., 1988). When regression diagnostic tests show a lack of both the normality of residuals and the homogeneity of variance, the cosinor approach has to be carried further by more appropriate models applied preferably to long as well as dense time series. Ultradians and infradians also characterize GH, among many other hormones.

The frequency of alterations such as spikes, the magnitude or area under a given spike, and an episode of GH can all be assessed in the context of the integrative circadian patterns. Furthermore, infradian-circadian modulations are demonstrated for mitotic activity as well. Infradians in rat cornea are a case in point (Tsai et al., 1987, 1989).

7. Time-microscopy of mitotic and related activity

On the left, Figure 12, the reproducibility of human mitotic rhythms published nearly a decade apart from different geographic settings is seen by the naked eye. Without curve-fitting different interpretations by the unaided eye alone are possible, including, for instance, emphasis on 2 peaks. With curve-fitting, the 24-hour amplitude assumption is rejected at the 1‰ level in each case and the acrophases are only 7°, i.e., 28 minutes apart. On the right, Figure 12 summarizes an analysis of circadian variation in murine pancreatic mitoses revealing self-explanatory acrophase differences in different functional units of the same organ (Halberg et al., 1973).

Figure 13 shows the transition in the systematic work carried out by the late Lawrence E. Scheving from the skin of his back, Figure 12, to the gastrointestinal tract and other systems of rodents, revealing drastic differences in amplitude of the rhythm in the incorporation of tritiated thymidine into the DNA at different anatomical sites, left, and an apparent gradient among differences in acrophase on the right of Figure 13. Figure 11 documents circadian aspects of nucleic acid formation and mitosis and lead to several rules.

1. As a group phenomenon, cell division undergoes a circadian rhythm here described for human babies and adults, growing and adult rodents and larval urodeles with widely differing amplitudes and phases at different anatomical sites. A laboratory assessment of the group rhythm in epidermal mitoses benefits from serially independent sampling with respect to both individuals and environments, since sampling at consecutive 4-hourly intervals from the same room, does not allow an approximation of the same average mitotic count 24 hours apart, as does sampling from separate rooms not previously disturbed by sampling from other animals (Halberg et al., 1959).
2. The epidermal mitotic rhythm (Figures 12 [left])

Figure 12 - ***left*** **Reproducibility of mitotic rhythm in adult human epidermis.** Fischer, mean number mitoses/1,000 cells. Scheving, mean number mitoss/1,000 cells (2,500-3,000 cells/specimen). Circadian rhythm in number of human epidermal mitoses. A majority of cell divisions in epithelial cells occur at a defined and predictable circadian system phase. Remarkable reproducibility of results obtained many years and miles apart. ***Right*** **Circadian acrophases of mitoses in 3 different functional systems** of mouse pancreas as well as of rectal temperature and liver glycogen. Rhythms with widely differing timing are found for the same variable -- cell division -- in the pancreas (in glucagon-producing A-cells, insulin-producing B-cells and exocrine acinar cells of the same organ) by curve-fitting procedures as well as by time plots. © Halberg.

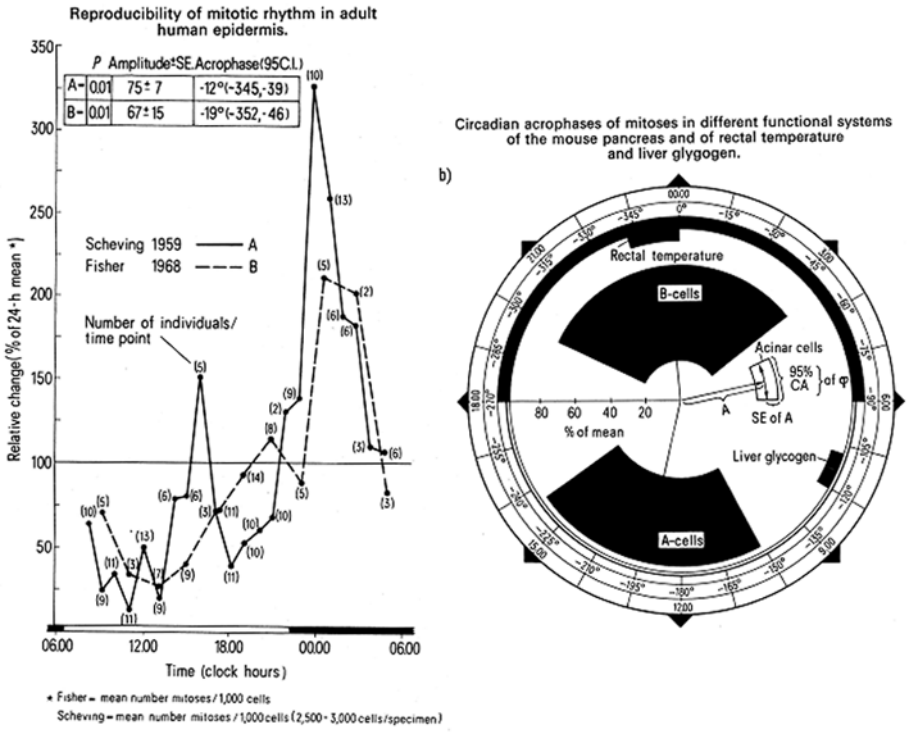
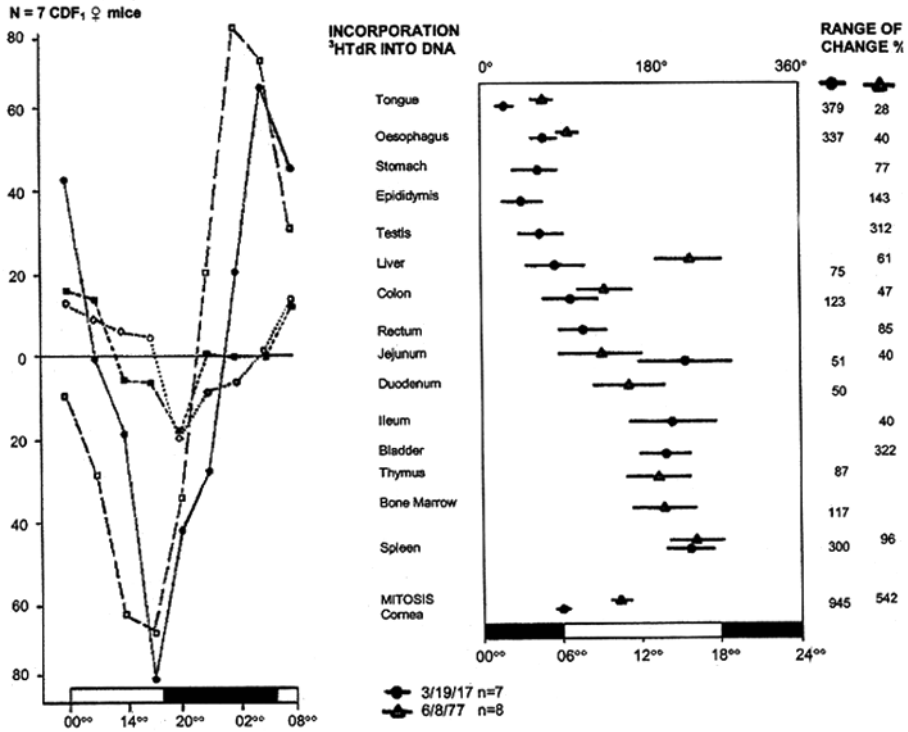


Figure 13 - Drastic differences in amplitude (left) and acrophase (right) of the circadian rhythm in the incorporation of tritiated thymidine into the DNA at different anatomical sites. The four curves (left) correspond to the esophagus (filled circles, solid line), ovary (filled squares, dotted line), tip of tongue (open squares, dashed line), and duodenum (open circles, dotted line). Original data of Lawrence E. Sheving. ©Halberg.



(a) in human adults, has characteristics reproducible by different authors years apart in different geographic locations (Figure 12) (Halberg et al., 1973);
(b) has a circadian amplitude larger in human adults than in babies, as assessed by serially independent sampling as to individuals, time and geographic sites;
(c) differs in its timing between nocturnally active rodents and diurnally active humans, while intermediate timing characterizes human babies as compared to adult humans or rodents, presumably because of extracircadian-over-circadian prominence and/or a lesser (if not lack of) 24-hour synchronization of rhythms,
(d) can be damped (reduced in amplitude) by

- a bilateral adrenalectomy (Halberg and Howard, 1958), or
- a hypophysectomy (Zander et al., 1954), or
- a growing breast cancer (Garcia-Sainz and Halberg, 1966), and

(e) can be amplified by deprivation of food and water, while
(f) it persists during exposure to continuous light or continuous darkness (Halberg and Barnum, 1961).

3. (a) The circadian rhythms in different functional units of the mammalian pancreas show different timing, in the glucagon-producing a cells vs. the insulin-producing b cells in the islets of Langerhans, and both also differ in phase form the circadian mitotic rhythm in the digestive enzyme-producing acinar cells (Fig. 12) (Halberg et al., 1973),
(b) differences in timing are also found among different sites in the gastrointestinal tract and among other systems in DNA labeling preparatory to mitoses (Cornélissen et al., 2002c);
(c) there is a differentiated mitotic coordination within an organ as well as within an organism as a whole in its different tissues and organs. (Fig. 13)
4. The circadian rhythms in epidermal, adrenocortical and hepatic rhythms
(a) can all be phase-shifted by shifting the temporal location of the LD12:12.
5. The circadian rhythms in liver parenchyma and/or skin epidermis
(a) can be frequency (24-hour) synchronized by manipulating a 12-hourly alternation of light and darkness (LD12:12 regimen), along with the circadian rhythm in count of circulating eosinophil cells, which then serves as a marker rhythm; the above-noted mitotic rhythms and the one in eosinophil count, all in phase with each other then differ in phase vs. the circadian mitotic rhythms in the adrenal cortex and in some other anatomical locations, such as certain functional areas of the pancreas. Frequency synchronization occurs with differences in phase that are zero or non-zero. As long as synchronization in frequency prevails, and any differences in phase are known, relatively simply determined rhythms, such as those in certain blood cell counts, can serve as markers.
(b) The adjustment after a shift of the temporal placement along the 24-h scale of the lighting regimen is slower in the epidermis than in the adrenal cortex, which in turn adjusts slower than the circadian rhythm of mitoses limited by being based in liver parenchyma, a finding based on two-timepoint sampling.

(c) Accordingly the internal timing among rhythms mapped in LD12:12 (with food freely available) does not hold during phase shifts of the lighting regimen; thus the role of the rhythm of circulating eosinophil cell counts as a marker for the circadian rhythm of mitotic counts in certain tissues, valid during 24-h LD12:12 synchronized conditions, does not hold during phase shifts of LD12:12. Limitations to the use of marker rhythms thus emerge.

(d) Internal timing under conditions of a free-run, e.g., by exposure to continuous light, continuous darkness or small meals at fixed equidistant intervals or by exposure to a non-synchronizing routine such as a 6-hour day of activity, meals or exercise, compatible with a circadian system of GH, under conditions rendered as constant as routinely possible on earth, differs from that during 24-hour synchronization in response to a prior synchronizer such as the lighting regimen or meals.

(e) Accordingly under constant conditions of light or darkness or after discontinuance of other synchronizing routines, the role of any marker rhythms remains to be examined in each case.

(f) In liver parenchyma, processes preparatory to mitoses involve a sequence of phospholipid labeling at the membrane, followed by RNA formation in the cytoplasm, preceding DNA formation by about 8 hours, which in turn precedes mitosis, with the qualification that RNA formation is also gauged in the fraction of cells that do not divide.

6. In the unicell *Euglena,* the absence of studies on synthesis available on mice is characterized by a lead of RNA content over DNA content. Here, the qualification necessary for growing rodent liver, that only some of the cells divide and that their behavior may be masked by non-dividing ones does not hold (Edmunds and Halberg 1981).

7. The effect of GH on hepatic mitoses
   (a) depends upon circadian stage at GH administration time (Halberg et al., 1973); and
   (b) the detection of a GH effect depends upon the stage of effect evaluation (Litman et al., 1958).
8. Depending on injection time, ACTH 1-17 can act upon DNA labeling in bone in a circadian periodic way so that, during the 24-h span after its administration, it is only stimulating throughout; inhibiting for a while followed by stimulation; inhibiting throughout; or stimulating for only a while followed by inhibition (Walker et al., 1985).
9. In the circadian dynamics of mitoses in urodeles:
   (a) in cornea, the rhythm is affected by epinephrine in a circadian stage-dependent way, inhibited at two circadian stages and raised at another stage;
   (b) in epidermis, the response to epinephrine is a rhythmic change from an inhibition of cell division to no-effect.
10. A magnetic storm, damps the circadian mitotic rhythm in mammalian cornea.

Whether the cornea is also a receptor of non-photic effects, apart from being a model for magnetic effects, remains to be investigated, in view of other magnetic storm effects not shown herein, that are in keeping with ocular reception of the effect. Specifically, magnetic storms are associated with changes in cardiac blood pressure (Chibisov et al., 2004; Chibisov, 2005) in laboratory animals, and cardiovascular frequency-specific effects in humans (Cornélissen et al., 1999, 2002a; Otsuka et al., 2001; Oinuma et al., 2002). Associated further with magnetic storms are changes in the circadian rhythms of murine circulating corticosterone (Jozsa et al., 2005) and in the concomitantly assessed MESOR and amplitude of the circadian melatonin rhythm in situ, namely both characteristics are increased in the hypothalamus and reduced in the pineal (Jozsa et al., 2005), in keeping with changes in human melatonin excretion (Burch et al., 1999; Weydahl et al., 2001).

8. Ultradian aspects

Blood samples of nine healthy subjects (six women and three men; in the age range of 26-49 years), collected every 4 h for 24 h, starting at 08:00 in the morning, show a 12-h component of serum osteoprotegerin (OPG) concentrations ($P = 0.038$) with peaks around noon and midnight (Tarquini R et al., 2005). No statistically significant circadian rhythm of OPG concentrations could be found by cosinor in this study group. PTH concentrations, not determined in this study, exhibit a circasemidian pattern along the 24-h scale; PTH may be tested as a putative determinant of the observed changes in serum concentrations of OPG, which serves as a soluble decoy receptor for RANKL inhibiting osteoclast formation and activity. PTH and glucocorticoids have been reported to decrease OPG concentrations, while estrogens, transforming growth factor b, a related bone morphogenic factor and thrombopoietin reportedly enhance the OPG production in osteoblasts and stromal cells of bone.

9. Leptin

Among the factors influencing bone mass, leptin, an eminently circadian hormone in laboratory animals (Fu et al., 2005), and in humans (Tarquini B et al., 1999, Tarquini R et al., 2003; Perfetto F.et al., 2004), has emerged as a mediator of bone turnover. Reportedly, leptin decreases bone remodeling in the mature skeleton, when trabecular bone turnover is high, by stimulating the osteoprotegerin (OPG)-RANKL-ligand pathway. Leptin also reportedly exerts negative effects on bone growth through a

hypothalamic pathway mediated downstream by the sympathetic nervous system. After binding to its receptor on hypothalamic neurons, leptin reportedly targets the osteoblast via the sympathetic nervous system (SNS) and osteoclast differentiation, via the SNS and cocaine- and amphetamine-regulated transcript (CART) (Ducy 2002; Takeda et al., 2002; Elefteriou et al., 2005). A remarkable aspect of leptin's coordination of bone mass is that its mediators do not affect leptin's other functions in animals that are unchallenged, i.e., fed with a normal diet. Indeed, mice unable to produce norepinephrine or mediate sympathetic signaling through the b2-adrenergic receptor (Adrb2) have a high-bone-mass phenotype but are lean and fertile (Takeda et al., 2002, Elefteriou et al., 2005). Likewise, mice lacking CART are osteoporotic but are lean on a normal diet and fertile (Elefteriou et al., 2005).

10. Clock genes and functional differences in intracellular morphology

Recently Fu et al. (2005) reported that CLOCK genes are also expressed in osteoblast cells, just as they are expressed in adipose and other peripheral tissues (Ando et al., 2005; Ptitsyn et al., 2006; Zvonic et al., 2006; cf. Roenneberg and Merrow, 2003; Zambon et al., 2003; Kobayashi et al., 2004; Li and Li, 2004; Yamamoto et al., 2004; Arjona and Sarkar, 2005; Iwanaga et al., 2005; Murphy et al., 2006; Watanabe T et al., 2006). These clock genes are present in peripheral tissues just as they are also found in the hypothalamic SCN (Reppert and Weaver 2001, meta-analyzed by Katinas et al., 2005). Fu and coworkers (2005) showed that circadian genes, *Period 1 and 2* (*Per 1*, *2*) display in osteoblasts a circadian pattern of expression. The model that they formulate from their results suggests that leptin, at the level of the hypothalamus, through signaling by b2-adrenergic receptors, first activates the transcription factor CREB then activates the peripheral clock and AP-1 genes in osteoblasts (conceivably apart from any effect on adipose tissue's circadian oscillators) which are also present (Ando et al., 2005; Ptitsyn et al., 2006; Zvonic et al., 2006). The clock genes reportedly inhibit osteoblast proliferation by inhibiting *c-myc*, which leads to *cyclin D1* "downregulation". Counteracting these effects, AP-1 genes promote osteoblast proliferation by "upregulating" *c-myc* and thereby *cyclin D1*. The clock genes reportedly exert influence in part because they also inhibit AP-1 gene expression.[3]

3 More generally, the use of terms such as "down" and "up" regulation implies effects upon the MESOR, which are best documented as such and in conjunction with effects upon other characteristics and, in the case of rhythmic endpoints, cannot be used based on spotchecks. Comparisons based on spotchecks can provide opposite "evidence" for both up and down regulation, depending only upon a sampling time, as a result of phase and/or frequency differences between the rhythms of two groups being compared, a situation that was clarified over half a century ago and led to Minnesota chronobiology (Halberg et al., 2003a).

Hughes et al. (2009) found two clusters of genes that cycle with 12- and 8-hour rhythmicity in liver, heart, kidney and lungs, harmonics of circadian gene expression, but ex vivo and under conditions of rescricted feeding.

We sought to explore an intracellular rodent chronome (time structure) as it represents a distribution of labor in time, and as it could serve as a marker for studies at the genetic level that could integrate the current findings of peripheral clock genes at the intracellular level. Johnson (1939) wrote about an "exceptionally substantial and durable self-winding and self-regulating physiological clock". A mechanism that was critical for the maintenance of a circadian rhythm was then found in the adrenal, leading on the one hand to circadian RNA and DNA rhythms and on the other to the brain (Halberg et al., 1951, 1958, 1959). Clock genes in the hypothalamus (Reppert and Weaver, 2001) were followed by peripheral clock genes in organs as a whole, such as the liver (Roenneberg and Merrow, 2003; Kobayashi et al., 2004; Yamamoto et al., 2004; Iwanaga et al., 2005); heart (Kobayashi et al., 2004; Yamamoto et al., 2004; Watanabe T et al., 2006); skeletal muscles (Zambon et al., 2003); adrenal glands (Watanabe T et al., 2006); lung, stomach, spleen, kidney and testes (Yamamoto et al., 2004); and cardiovascular systems (McNamara et al., 2001). Coordination between central and peripheral clock genes is also discussed (Roenneberg and Merrow 2003; Li and Li 2004). Fewer publications are devoted to clock genes in specific cells: in osteoblasts (Fu et al., 2005), natural killer cells (Arjona and Sarkar, 2005) and fibroblasts (Murphy et al., 2006). Thus, the time came to turn away from a master clock illusion (Powell, 1988; see also Cornélissen et al., 1988).

Since every organ is multifunctional, being composed of many also multifunctional tissues, and every tissue is composed of various multifunctional cells, it was reasonable to look at clock genes in osteoblasts. They already show a difference in timing of cellular peripheral oscillators vs. a central hypothalamic oscillator. But the **organs** are still made up of **tissues** and ultimately of **cells** that are the primary functional units. Lashko et al. (1975) and Lashko (1977) investigated C_{57} white mice allowed to feed freely only during the daily light or dark span and measured the height of parts of the cells, which contain different organelles responsible for different intracellular functions (Krstic, 1984) as well as total cell length. Analyses were performed at the chronobiologic "macroscopic" level. Primary measurements were secondarily analyzed by "time-microscopic" statistical methods (Katinas and Halberg, in press). Results and analysis of circadian spectral components reveal, at the cellular level, differences in timing of various cellular functions at the intestine's brushed (or striated) enterocytes. Those cells absorb substances from the lumen of the small intestine, metabolize them and excrete into underlying connective tissue and into the capillaries.

The timing of the various organelles, responsible for those functions, reveals an orderly gradient sequence in functional activity of organelles: there is a phase difference of about 11 hours between the activity of the brush border (responsible

for intake of products from the intestinal lumen) and the basal zone mitochondria (responsible for the output into neighboring capillaries of an energy supply). Acrophase mapping can serve as a marker for the analysis of mechanisms of coordination among the central clock genes and peripheral clock genes in the real "workers", namely cells. Whether the central and peripheral clock and other genes, that may alternate in importance in a collateral hierarchy and may shed light on the problem of the mechanisms of coordination between local peripheral (intracellular) clock genes and other functional (not "clock") genes responsible for specific partial functions of the membrane and in organelles of the cell.

Since each cell has many functions, there should be multiple coordination mechanisms. Gene timing should correspond to functional timing. One can postulate, as one hypothesis, a different timing of various organelles (which provide various functions of the cell) that need a temporal coordination of different pathways from the intracellular pacemaker (clock genes) to the functional genes, responsible for those functions. These pathways need to be investigated. An alternate hypothesis is that different functions of the cell depend upon different specific intracellular pacemakers. If so, the peculiarities of those pacemakers need to be investigated.

In any event, it is not quite enough to examine the peripheral clock genes relating them to organs, to tissues or even to a cell as a whole, but it will be necessary to relate them to really functioning entities, i.e., to the various components of cells. But whether the peripheral genes today are complemented by special intracellular timing genes or whether the peripheral genes will act only at one or a few points in sequences of different functional events, intracellular timing can only add to an understanding of our physiology and perhaps the simple rule of thumb of what comes first in each functional cycle matters, and in that context, there is a hint from the circadian melatonin rhythm in situ in the duodenum vs. that in the plasma hypothalamus and in the pineal. More often than not, a circadian rise in melatonin gets up first in the gut in two species, and thus far it never lagged in any species. The gut may be a fertile field to look at what peripheral clock genes do at the intracellular level (Hoogerwerf et al., 2006).

11. Circaseptans may complement circadian and ultradian focus in the study of growth

Elsewhere we demonstrate that the same total dose/week of an immunomodulator, lentinan, can have dramatically different effects upon a (malignant) growth as a function of its circadian and circaseptan (about 7 -day) administration pattern (Halberg E and Halberg F, 1980). This is hardly surprising since it has already been demonstrated that the same dose of a hormone can stimulate or inhibit DNA labeling

as a function of circadian stage (Walker et al., 1985). Research carried out in the clinic may follow-up on the findings that show the drastically different fashion in which one or another molecule given in a fixed dose determines growth as a function solely of the now resolvable and shown to be interactive multifrequency components in a spectrum of rhythms with different frequencies.

About 7-day growth response. Multiseptans are relatively prominent in the rodent's compensatory renal hypertrophy, following a unilateral ligation of the renal artery or unilateral nephrectomy (Hübner 1967). A circaseptan pattern is also seen in a study of the responses of hepatic variables to growth hormone studied by Nettesheim and Oehlert (1962) and meta-analyzed by Halberg and Cornélissen (1994; cf. Halberg, 2000; Cornélissen et al., 2002b). Whereas in most cases the ratio of about 7-day and about 3.5-day amplitudes (in the numerator) and of circadian amplitudes (in the denominator) is smaller than unity (the circadian amplitude in the denominator is slightly larger than the multiseptan amplitude in the numerator), the multiseptans can actually be more prominent than the circadian.

12. Infradian variations in murine dentin accretion and the suprachiasmatic nuclei (SCN)

Figures 14a-b show changes in dentin of a control rat kept in continuous light. Both circadian and circaseptan changes are visible to the naked eye. Figure 14c shows the circadian effect of the suprachiasmatic nuclei (SCN) upon murine growth indicators: bilateral ablation is compatible with rhythm persistence with changes in characteristics for DNA labeling and mitoses (Halberg et al., 1979; Cornélissen and Halberg, 1994), albeit not with persistence of a circadian rhythm in dentin accretion (Ohtsuka-Isoya et al., 2001). The effect on the circadian A is a reduction (with the exception of the stomach) and an effect on ϕ is an advance at the cellular level and in core temperature by cosinor methodology, although the rhythm seems to be lost in this variable when timeplots are viewed (Osborne and Refinetti, 1995; Refinetti et al., 2006).

With respect to the chronome of daily accretion measured by tissue densitometry and by dividing the distances between markings from dye applied at known intervals into equal time intervals, Figures 14a-c each show a circaseptan A larger than the circadian A in controls, so that the A ratios are 1.4 and 2.4, respectively. Figure 14c shows a still larger ratio of 2.86 after SCN ablation, which is diluted in this figure by a fit to all data, to the shorter span before operation and to the longer span after removal of both SCN (Shinoda et al., 2003).

The naked eye cannot miss the increase in infradian A after surgery, accompanied by a frequency multiplication of the circadian component, a phenomenon dubbed by us a spectral compromise (Shinoda et al., 2003). It is

Figure 14a - The dentin formation of a rat monitored before and after a sham-operation, kept in continuous light, is characterized by a prominent infradian if not circaseptan component, with an amplitude larger than that of the circadian rhythm (Shinoda et al., 2003). © Halberg.

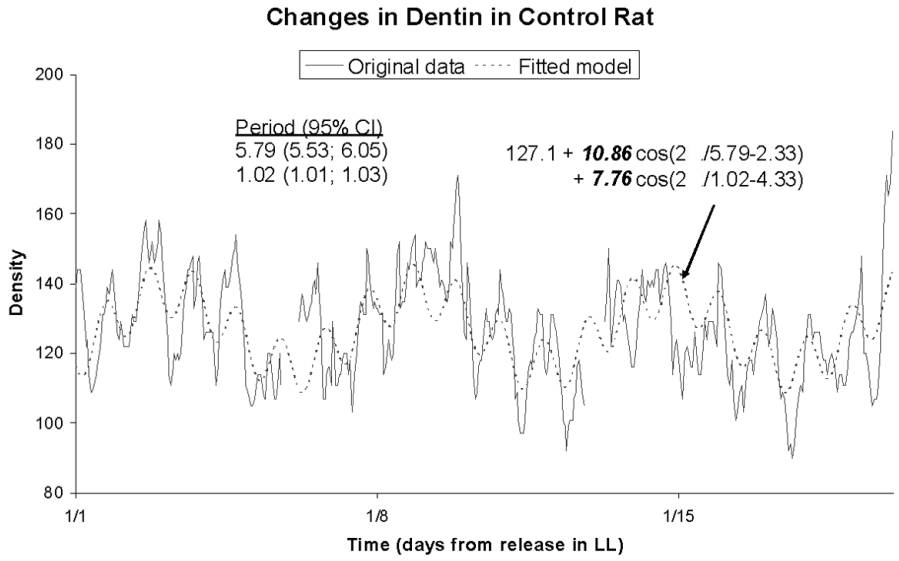
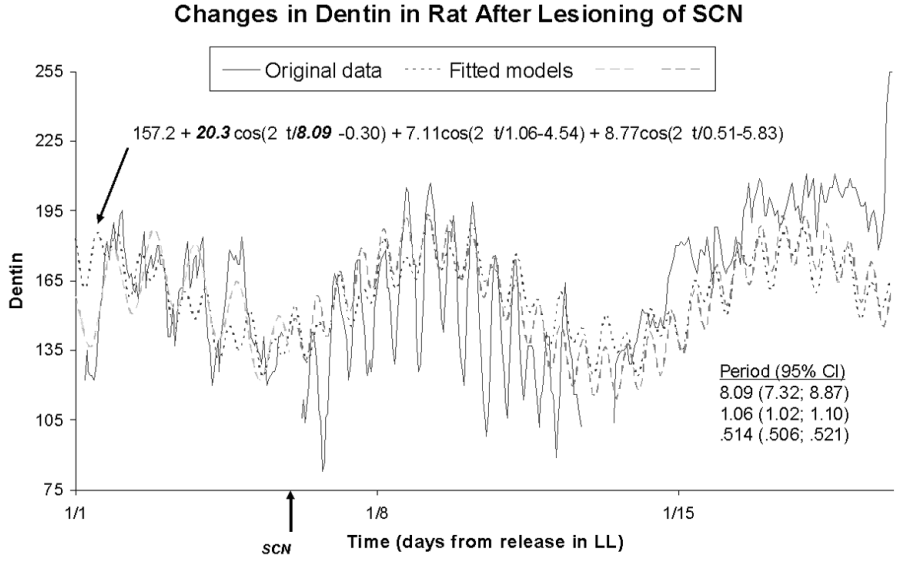
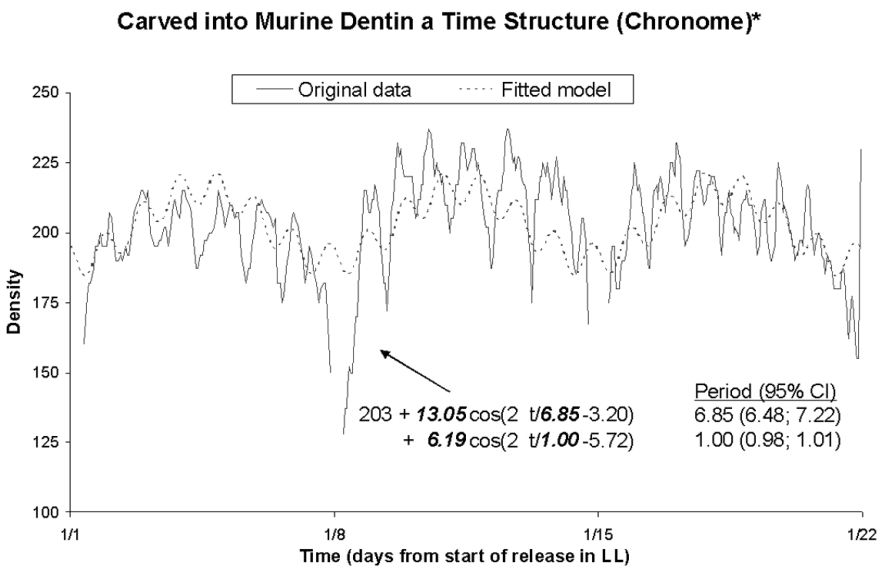


Figure 14b - The dentin formation of a rat monitored in continuous light without surgery is characterized by a prominent circaseptan component, with an amplitude larger than that of the circadian rhythm (Shinoda et al., 2003). © Halberg.



challenging to investigate why, in growth gauged in teeth, the circaseptan A is more pronounced than the circadian A to start with and, further, why the ablation of the 2 SCN in Figure 14c, brings about its multiplication first with a 12-hour component and a time-macroscopic loss of the circadian pattern thereafter, while a very prominent infradian pattern persists. For circadian-infradian relations, the two SCN may inhibit infradians. Multiseptans have also been studied in enamel as the thickness between two consecutive brown striae of Retzius (Appenzeller et al., 2002; Halberg et al., 2002), with the possibility in mind that a neuroendocrine chronome of a spectral record in ancient teeth can trace the behavior of populations millennia ago.

Figure 14c - The dentin formation of a rat monitored before and after the ablation of the suprachiasmatic nuclei (SCN), kept in continuous light, is characterized by a prominent infradian if not circaseptan component, with an amplitude larger than that of the circadian rhythm. An infradian over circadian prominence is also observed in a separate analysis, using the data collected only after SCN lesioning (Shinoda et al., 2003). © Halberg.



* With a larger about-weekly (circaseptan) and about-half-weekly (circasemiseptan) than about-daily (circadian) amplitude in male Wistar rat transferred from LD12:12 to continuous light for 4 weeks (shown are last 3 weeks 'carved' into an incisor's transverse section); Patterns uncovered by densitometry in space.

13. About-monthly variation in neonatal height and weight

In focusing first on populations, Garcia Alonso et al. (2000) report on birth weight and length of 635 Spanish babies measured between November 1978 and April 1990. The transverse neonatal data series thus obtained was analyzed by single cosinor, least squares spectra and nonlinear rhythmometry. In the least-squares spectra computed on the original data, an about-monthly component is found for height at birth (P=0.006) and for birth weight (P=0.003). This component is resolved by nonlinear least squares. Its period is estimated to be 28.11 days (95% CI: 28.02; 28.20 days) for height at birth and 28.00 days (95% CI: 27.92; 28.09 days) for birth weight. The corresponding double amplitudes are 0.70 (95% CI: 0.04; 1.36) cm and 187 (95% CI: 35; 339) g. These components are visualized by plexogram. A time (of month) effect is further validated (at the 10% probability level) by one-way ANOVA in each case (height at birth: F=1.973; P=0.068; birth weight: F=2.683; P=0.014). Scrutiny by chronobiologic serial section indicates that the acrophase of this about-monthly component is relatively stable during the overall study span, even if there are very large amplitude fluctuations. In this analysis, the data are analyzed at a trial period of 672 hours (4 weeks) using an interval of 4,032 hours (24 weeks), which is progressively displaced in increments of 168 hours (1 week) throughout the time series. Statistical significance is reached during relatively long spans, as shown by the dots bracketing the acrophase sequence, their distance representing the corresponding 95% confidence interval when the zero-amplitude (no-rhythm) hypothesis is rejected.

The circannual components characterizing height at birth and birth weight are in keeping with a similar component reported for the height at 18 years of age of 587,125 Austrian recruits, peaking in April (Weber et al., 1998).

The presence of a prominent about-monthly component with a period approximately matching those of the synodic, tropical and anomalistic lunar periods, but slightly longer than that of the current rotation period of the sun around its axis, deserves further study, preferably in prospective studies of cohorts of infants followed-up longitudinally in different geographic locations where putative geomagnetic and gravitational interactions may be of different intensity, yet in view of a built-in menstrual cycle in women and a circatrigintan periodicity in man (Santorio, 1657; Halberg et al., 1965), a built-in population rhythm is also considered herein as a realistic possibility.

The change with an about-monthly period would in theory be intrinsic to the baby, as a member of a population only (since each baby contributes just one value to this population rhythm) or it could represent an environmental effect only or both. It is the more noteworthy that a neonatal circatrigintan rhythm has an approximate, just discovered counterpart, emerging from our meta-analysis of data from a study carried out on a method for estimating the surface area of the human body by Weinbach (1938). He provided many original values from measurements

made every few days, 37 during the first year of life separately on boys' and girls' growth. A spectral analysis of his data in Table 3 shows that of 8 variables, the likelihood of a chance effect in each case is smaller than 17% and in 3 cases is smaller than 5%, and in still other cases at or below 10%.

In viewing this meta-analysis as a whole, one must conclude that a decade before the usual menarche in girls and before adrenarche in both sexes, body length and right thigh girth in boys and body surface in girls, and most likely all variables studied by Weinbach (1938), including weight, height, right thigh girth and body surface undergo an about 30-day (circatrigintan) rhythm, a finding also in keeping with the finding over only a single cycle of an infradian cycle of similar length in the human neonatal circulation (Watanabe et al., 2003).

14. Circasemiannual, circannual and neighboring spectral components

Garcia Alonso et al. (1993) reviewed the early literature and provided an analysis of measurements made monthly between birth and about 15 months of age. Population-mean cosinor analyses showed highly statistically significant circannual and circasemiannual components ($P<0.001$) by reference to time of birth for both height and weight (Tab 4). With respect to calendar time, a circannual component is detected for height ($P=0.004$), but not for weight ($P=0.189$); the circasemiannual component is not statistically significant for height ($P=0.431$) or weight ($P=0.773$), Table 5. Even in the case of the statistically significant circannual component of growth in height, the rhythm is detected with greater accuracy when the date of birth rather than calendar-time is used as the reference. It thus appears that in young children the circasemiannual and circannual changes in the rate of growth rather than a mere function of the calendar year's seasons are more determined by the time of birth and this may depend on age rather than mainly on season.

If nurture, the seasons, temperature and other features associated with the change in seasons were the only critical factor in circannual rhythmicity, no rhythmicity in relation to the date of birth would be anticipated. The results of population-mean cosinors demonstrate the congenital if not built-in aspects of about-yearly and about-half-yearly component in human infantile growth in length and gain in weight, in keeping with the postulation of a built-in chronome, defined as the time structure consisting of rhythms and trends and what thus far could not be evaluated, chaos, that can generate rhythms (Goldbeter 1996; Gonze et al., 2004). Subsequent analyses suggest in addition the presence of a 1.3 transyear in the data of Garcia Alonso et al. (1993) detected by one of us (DH). A longer-than-calendar-yearly component is also found in longitudinal monthly data from 13 to 72 months

Table 3: Chronome (time structure) of change in infants' characteristics during first 4 years of life*

Change in (units)	Period (h)	PR (%)	P	MESOR ± SE	Amplitude ± SE	Acrophase ± SE
Boys						
Weight (kg/y)	830.90	4	0.141	3.61 ± 5.47	15.09 ± 7.71	-100° ± 29
Height (cm/y)	789.73	6	0.049	9.28 ± 17.45	61.73 ± 24.21	-287° ± 23
Girth (right thigh)	739.75	7	0.027	9.02 ± 12.82	47.74 ± 18.22	-163° ± 22
Body Surface (cm2/y)	742.88	6	0.061	13.05 ± 23.22	77.34 ± 31.70	-8° ± 25
Girls						
Weight (kg/y)	789.73	3	0.169	3.96 ± 3.92	10.89 ± 5.68	-276° ± 28
Height (cm/y)	715.59	4	0.103	9.17 ± 12.21	38.49 ± 17.23	-198° ± 26
Girth (right thigh)	752.44	6	0.051	14.69 ± 12.66	44.54 ± 17.67	-237° ± 23
Body Surface (cm2/y)	690.23	6	0.039	27.21 ± 17.32	61.03 ± 25.74	-144° ± 22

*Data from Weinbach A.P. (1938), A simple method for estimating the surface area of the human body from birth to maturity, Growth 2: 303-317.

Table 4: Circannual and circasemiannual components of birth weight and length*

Variable		1.0-year			0.5-year			Overall	
(units)	M±SE	P	2A±SE	ϕ±SE	P	2A±SE	ϕ±SE	PR	P
Height (cm)	50.58±0.07	0.0046	0.60±0.19	-135°±18	0.165	0.41±0.19	-284°±27	67	0.066
Weight (g)	3381±15.3	0.082	117±43	-121°±21	0.081	117±43	-278°±21	68	0.065

M: MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm), a rhythm-adjusted mean
2A: double amplitude, a measure of the extent of predictable change within a cycle
ϕ: acrophase, measure of the timing of overall high values recurring in each cycle; expressed in negative degrees, with 360° equated to period length and 0° set to 00:00 on Sunday 25 Dec 1977
SE: standard error
P: P-value from test of zero-amplitude (no-rhythm) assumption (separate contribution of each of the two components included in the model) and from the assessment of overall adequacy of model derived by F-test (overall model)
PR: percent rhythm (proportion of overall variability around the mean value which is accounted for by the fitted model)

Table 5: Circannual rhythm in neonatal growth determined by baby's age rather than seasons*

	Reference time	P*	Acrophase (95% CI)
1 year			
Weight	Time of birth	<0.001	-137° (-126, -148)
	December 22	0.189	-4° ( )
Height	Time of birth	<0.001	-124° (-114, -134)
	December 22	0.004	-282° (-230, -335)
0.5 year			
Weight	Time of birth	<0.001	-233° (-209, -255)
	December 22	0.773	-189° ( )
Height	Time of birth	<0.001	-202° (-172, -231)
	December 22	0.431	-23° ( )

*P-value from zero amplitude (no-rhythm) assumption.

Table 6: Chronome (time structure) of change in infants' height and weight during first 6 years of life*

A. Multiple-component cosinor fit of anticipated components detected in least-squares spectrum						
Change in	Period (y)	MESOR ± SE	PR	P	Double amplitude ± SE	Acrophase (ϕ) (95% CI)
Height (cm)		0.78 ± 0.06				
	2.00		4	0.033	0.41 ± 0.16	-74° (-30, -117)
	1.30		4	0.074	0.36 ± 0.16	-64° (-17, -112)
	1.05		6	0.017	0.46 ± 0.16	-102° (-64, -140)
	0.50		4	0.044	0.39 ± 0.15	-82° (-37, -126)
	Overall		17	<0.001		
Weight (g)		192.1 ± 16.7				
	2.00		3	0.077	108.0 ± 47.6	-79° (-28, -129)
	1.30		4	0.055	117.8 ± 48.8	-73° (-28, -118)
	1.05		5	0.027	131.5 ± 47.5	-107° (-67, -147)
	0.50		2	0.282	75.0 ± 46.9	-56° (-346, -127)
	Overall		14	0.008		
Acrophase expressed in (negative) degrees, with 360° ≡ period length and 0° = time of birth.						

B. Nonlinear validation of near-transyear (analyses on residuals from second-order polynomial)			
Changes in	MESOR (95% CI)	Period (y) (95% CI)	Double Amplitude (95% CI)
Height (cm)	0.81 (0.68, 0.94)	1.075 (1.004, 1.158)	0.40 (0.02, 0.77)
Weight (g)	221.6 (183.3, 259.9)	1.071 (0.978, 1.180)	84.0 (, 193.2)

*Data from Baldwin B.T. (1921), The physical growth of children from birth to maturity, 60-63, 255-257. University of Iowa Studies in Child Welfare 1:1.

**Changes during first year of life slightly different from older ages. Least squares spectra of data excluding those during first year of life show similar spectral peaks, albeit accounting for a smaller proportion of the overall variance; period estimate of near-transyear only slightly affected by inclusion of second-order polynomial in model. Statistical significance for a calendar-yearly component for either change in height (P=0.167) or weight (P=0.124) was not reached (not shown).

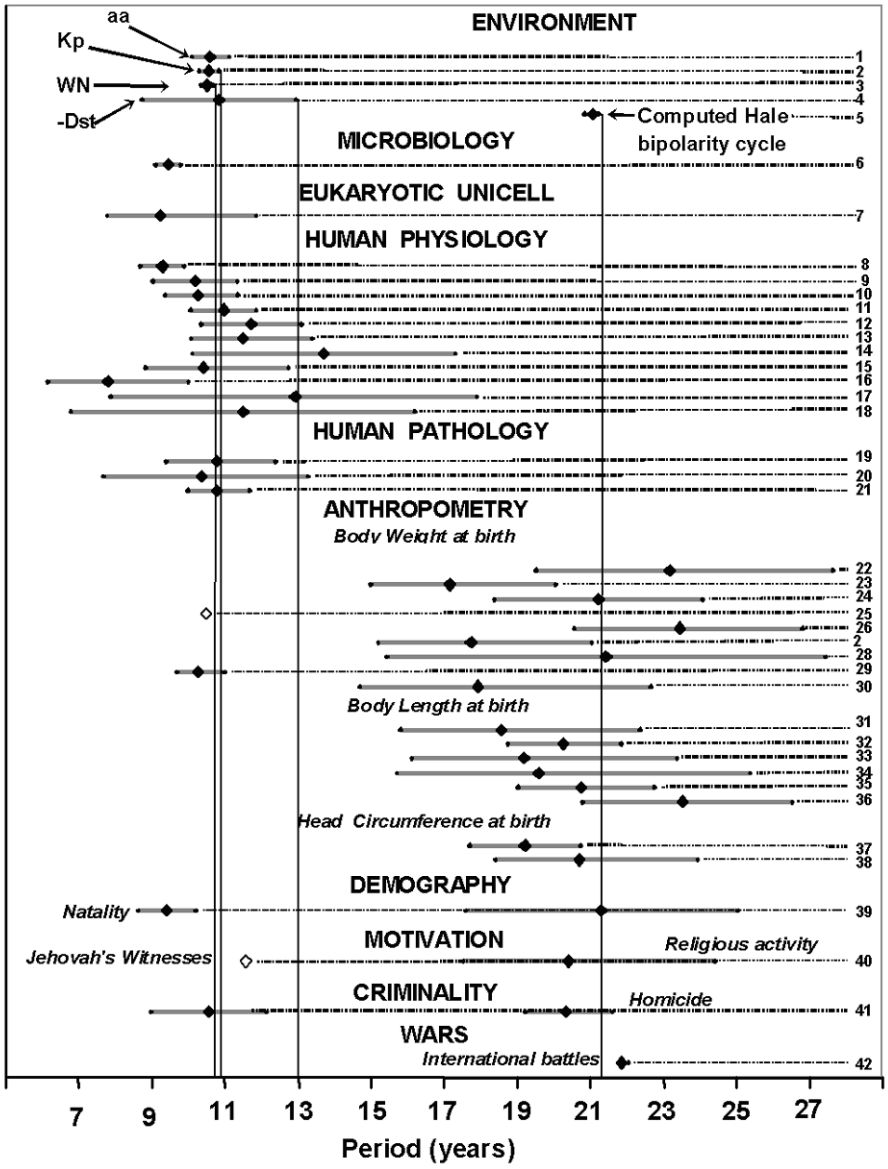
of age collected by Bird T. Baldwin (1921) by analyses summarized in Table 6. A calendar-yearly circannual component is also found cross-sectionally in the data measured at birth by Garcia Alonso et al. (2000)

15. Circadecadals, circadidecadals and circamultidecadals

Figure 15 shows periods between 10 and 20-year length for cycles in physical environmental factors, on top, and in biology, including auxological series, below. The length of the data analyzed differs greatly among the time series of physical cycles as well as among the biological cycles and the condition of comparing contemporaneous time series is violated in this attempt to show a degree of generality of the periods involved. Charts wherein the spans covered by the biological and physical data are the same are preferred whenever possible. There are also differences in the density of a 2,556-year length for international battles, a 112-year length for the case of a series of neonatal dimensions from Moscow, and still other much shorter but sometimes denser series. A discussion of relations among reciprocal periods will have to be based in each case on analyses of coincident time spans documented with equal density, since the environmental periodicities are highly variable, as documented for the Schwabe cycle gauged by the Wolf's relative sunspot numbers elsewhere (Cornélissen et al., 2000; Halberg et al., 2006a and b and in press). Only with this caveat are the indicated periods presented in Figure 15.

Elsewhere the spectral behavior of 3 biological, one geophysical and 2 solar activity cycles during identical spans has been analyzed and remarkable coincidences in the major components of Schwabe and Hale as well as geophysical antipodal (aa) cycles on the one hand and human blood pressure and heart rate measured about 5 times each day for 38 years have been found (Sothern et al., 2005). In the same clinically healthy man's heart rate and systolic and diastolic blood pressure, the three major spectral components have environmental counterparts with overlapping CIs (Halberg et al., 2005b and 2006c). In addition to these periods of corresponding length (Halberg et al., 2006a and b), associations are suggested by similar changes of phases in time and there are also results from an approach by subtraction and addition. That these associations are not an effect solely of the sun is documented by phase relations of the about 21-year cycle such as a particularly prominent difference in phase that characterizes cycles of similar length in the neonatal body weight of over two million children in Minnesota vs. the contribution of one million children's body weight and length in Denmark and smaller populations elsewhere. The role of telluric or atmospheric currents is pertinent in this context, but the numbers involved leave little doubt that the cycles are real and require much further study over many more cycles.

Figure 15 - Partial chart of variables, including neonatal anthropometric measures, exhibiting cycles with periods of about 10.5 and 21 years. © Halberg.



Neonatal Body Length

This opportunity was offered by the late Dr. Boris Nikityuk (Halberg et al., 2001b): Body length at birth was recorded annually from random samples of 25-150 babies in Moscow, Russia, during the span from 1874 to 1985, separately for boys and girls. Each data series was analyzed by the linear and nonlinear cosinor (Halberg 1980), with a model consisting of a first-order polynomial and two cosine curves with trial periods of ~50 and ~20 years. All three components were found to be statistically significant, as attested by the non-overlap of zero by the CI (the 95% confidence intervals) for the slope of the linear trend and for the amplitudes of the two periodic components. Over the 112-year span and the geographic site examined, the body length for both boys and girls can be characterized by a decreasing trend and an about-50-year cycle, with a secondary spectral peak at a frequency of one cycle in about 20 years, the latter corresponding in general terms to the Hale cycle of sunspot bipolarity, with the CI of the period given in parentheses.

Specifically, for the boys the slope was -0.018 (95% CI: -0.026; -0.011) cm/year, and for the girls it was -0.017 (95% CI: -0.024; -0.009) cm/year. The longest infradian period (in years) was 52.72 (95% CI: 46.97; 58.47) for boys and 51.15 (95% CI: 44.84; 57.46) for girls. Its double amplitude (in cm) was 1.64 (95% CI: 0.98; 2.30) for boys and 1.52 (95% CI: 0.80; 2.24) for girls. The other infradian component had a period (in years) of 20.28 (95% CI 18.76; 21.86) for boys and 20.76 (95% CI: 19.05; 22.78) for girls. Its double amplitude (in cm) was 0.84 (95% CI: 0.22; 1.46) for boys and 0.84 (95% CI: 0.16; 1.52) for girls. A smaller peak in the least squares spectrum around one cycle in 7 years was not validated nonlinearly, but is hardly surprising as the third harmonic of the Hale cycle. A very close agreement between boys and girls for the point and interval estimates of the slope and of the period lengths and double amplitudes of the two periodic components indicates that changes in body length at birth followed a very similar pattern in both genders in the geographic/geomagnetic setting of the time investigated. Girls are on the average smaller than boys, as documented by the non-overlap of the 95% CIs of the MESOR for girls (51.57; 95% CI: 51.33; 51.81 cm) and for boys (52.21; 95% CI: 51.98-52.43 cm). The great similarity between boys and girls in the time course of body length at birth is supported by a correlation coefficient ($r=0.849$). A relation between body length and birth weight is statistically significant for boys and girls (boys: $r=0.589$; $P<0.001$; girls: $r=0.521$; $P<0.001$). The about 20.5-year cycle is hence also in keeping with a possible modulation of body length at birth by the solar activity cycle.

The foregoing sample over a long span can be aligned with a much shorter time series of a much larger sample of over 1,000,000 babies' body length at birth in Copenhagen, Denmark. The circadidecadal component is most prominent with an amplitude exceeding by far that at a trial period of one year, the sole concern of the original authors (Wohlfahrt et al., 1998; cf. Halberg et al., 2003a). The length of babies from Kazakhstan also shows prominent circadidecadals, while for one sex in one geographic location (Kazakh boys), the circadecadal amplitude is larger than the didecadal one.

Head Circumference

Neonatal head circumference was also available from Boris Nikityuk as yearly averages from the same presumably random samples of 25-150 babies of each gender between 1874 and 1985 in Moscow, who provided the neonatal body length. As in the case of body length at birth, head circumference at birth is smaller for girls (35.13; 95% CI: 34.93; 35.34 cm) than for boys (35.59; 95% CI: 35.38; 35.80 cm) ($P<0.01$).

Least squares spectra reveal a prominent component with a period of about 60 years for boys and about 80 years for girls. In addition, an about 20-year component again constitutes a secondary peak in the least-squares spectra. A model including these two components was further tested and validated nonlinearly for boys and girls, as shown by the non-overlap of zero by the 95% CIs for the amplitude of each tested component. For boys, the model resolved nonlinearly consists of an infradian component with a period of 58.83 (95% CI: 52.28; 67.32) years and a double amplitude of 1.38 (95% CI: 0.76; 2.00) cm, and of another infradian component with a period of 19.23 (95% CI: 17.71; 20.75) years and a double amplitude of 0.80 (95% CI: 0.18; 1.42) cm. For girls, the corresponding model is characterized by an infradian component with a period of 87.18 (95% CI: 69.94; 104.52) years, with a double amplitude of 1.12, (95% CI: 0.56; 1.68) cm, and another infradian component with a period of 20.73 (95% CI: 18.42; 23.95) years, with a double amplitude of 0.44 (95% CI: 0.001; 1.02) cm.

With the data available, the 95% CI of both periodic components are quite broad. Nevertheless, the nonlinear results indicate that the about 87.2-year cycle resolved nonlinearly for the girls may be longer than the about 58.8-year cycle resolved for the boys, as observed by the non-overlap of their 95% CIs. A plot of the data as a function of time reveals, however, that, contrary to body length at birth, in the case of neonatal head circumference, the second cycle has a much larger amplitude than the first cycle of the longest infradian component. Moreover, the first cycle, while damped for the boys, is practically absent for the girls. This discrepancy between boys and girls may account, at least in part, for the difference in the estimated period length. A correlation analysis of neonatal head circumference between boys and girls shows a relatively close association ($r=0.842$; $P<0.001$), supporting the proposition that differences in period length may in fact result from an asymmetry between the first and second cycle of the about 60-year component in the case of neonatal head circumference. Although statistically significant, the correlation between neonatal head circumference and birth weight (boys: $r=0.386$, $P<0.01$; girls: 0.289; $P=0.01$) or body length at birth (boys: $r=0.309$, $P<0.01$; girls: $r=0.317$, $P<0.01$) is much less pronounced, a result suggesting the presence of trends not only in one or the other measure of human birth statistics, but also in their interrelationships.

Birth Weight

In turning again to the Nikityuk series, a major component of variation common to boys and girls is an about 63-year cycle, validated nonlinearly. An about 10.2-year

cycle (P=0.010) was validated nonlinearly for the girls, but not for the boys. Other components found in the least squares spectra were not anticipated and differed between boys and girls. Although the data series are still limited for an investigation of changes along the scales of a century, one component that remains consistent for the different indices available (neonatal body length and head circumference and also birth weight) relates to the about 20-year component and its second harmonic with a period of about 10.2-years, which is in keeping with a modulation of human neonatal morphology by the solar activity cycle. Moreover, there is an even longer series covering 120 years from Norway by Margit Rosenberg (1988) demonstrating, upon meta-analysis, a circadecadal component in birth weights in three university hospitals. As in the case of body length, there is a large but short series on body weight from Denmark and another series of over 2 million babies from Minnesota. In these series at different latitudes, as compared to Moscow, Oslo and Bergen, the didecadal component is most prominent and again exceeds in extent of change any about-yearly effect usually considered in the conventional literature (Weber et al., 1998; Wohlfahrt et al., 1998).

A Non-photic "Switch": Heliogeomagnetics?

A decadal 10.2-year component had been reported for the Ap and aa indices of magnetic disturbance during a 103-year span starting in 1868 (Delouis and Mayaud 1975), thus approximately matching the observation span of Boris Nikityuk's and Margit Rosenberg's investigation. Although not necessarily causal, this numerical association warrants further study of possible environmental effects beyond light and temperature in neonatal morphology. This is the more pertinent since neonatal blood pressure and heart rate have been reported to be resonant with about 7-day cycles in the local geomagnetic index K in Moscow (Syutkina et al., 1997) and to undergo changes matching the solar activity cycle (Syutkina et al., 1996), whereas their endogenicity has been documented by free-running in adulthood (Halberg et al., 1965). Whereas more work is needed to understand why girls and not boys exhibit an about 10.2-year cycle in birth weight, there are precedents for anthropological differences between boys and girls (Grande et al., 1994).

16. The biological decade and double decade

We can also turn to the degree of generality of chronome components such as the about 10.5- or about 21.0-year cycles in additional data on the circumference of chest and abdomen at birth in Moscow (Russia), as well as in data on weight, height and head, chest and abdomen circumference at birth of Russian and Kazakh babies born in Alma-Ata (Kazakhstan). The extent of synchronization of these two components with periods of about 10.5 and 21 years can be examined among

variables in different populations living in the same or in different geographic and geomagnetic locations.

After detrending, estimates of the amplitude and phase of the 21-year Hale and the 10.5-year Schwabe-like cycles were obtained by the least-squares fit of cosine curves with trial periods of 21.4 and 10.2 years, respectively (corresponding to spectral peaks of Wolf's number estimated since 1749 and of Kp, recorded since 1932). Results were summarized by population-mean cosinor (Halberg 1969) to examine the extent of synchronization of these two components among the different data series.

The about 21.4-year component was found to be statistically significant for height and head circumference in Moscow, as well as for chest circumference in Moscow and for weight and height in Alma-Ata (and incidentally also for neonatal weight in Minnesota). The about 10.2-year component was detected with statistical significance only for the weight of girls in Moscow and for the height of boys in Alma-Ata. The phases of both components show a tendency to cluster when summarizing results from all data series (21.4-year component: $P=0.056$; 10.2-year component: $P=0.055$), peaking, respectively, about 13.7 and 9.0 years after the reference time (January 1874) with recurrence every 21.4 and 10.2 years, respectively. A summary of all birth statistics recorded in Alma-Ata (20 series) reached statistical significance in the case of a 21.4-year component ($P=0.003$), peaking about 16.6 years after the reference time, and borderline statistical significance in the case of the 10.2-year component ($P=0.094$), peaking 7.5 years from the reference time. By comparison, birth statistics in Moscow showed a similar pattern both in the case of the 21.4-year component ($P<0.001$) peaking 8.7 years from the reference time and in the case of the 10.2-year component ($P=0.005$) peaking 0.3 year from the reference time. The 7.9-year difference in phase of the 21.4-year component assessed in Alma-Ata vs. Moscow is statistically significant, as attested by the non-overlap of their 95% confidence intervals.

The above-mentioned clustering of phases suggests some degree of synchronization of the Hale and Schwabe cycles among different birth statistics recorded in different geographic locations and thus a planetary effect. Separate analyses in Moscow and Alma-Ata, however, reveal a difference in phase for the 21.4-year component. Several limitations should be considered in interpreting the results of this study. First, any magnetic disturbance effects on birth statistics constitute at best one among several environmental influences. Second, some of the data series cover at best two cycles of the Hale component, thus rendering the estimation very difficult. In other words, both the amplitude and phase estimates are associated with a relatively large uncertainty. This is the more so since the presence of even longer-term trends in some of the data series required them to be detrended prior to analysis. Even a limited second-order polynomial trend may have affected the estimation of the two components of interest herein, i.e., of a biological decade and double decade.

An influence of geomagnetic disturbance on birth statistics is further supported by cross-spectral coherence (CSC). CSCs have in common with correlation coefficients that they describe the relation between two variables. They are less unspecific in that they describe the relationship at a certain frequency. To avoid listing spurious associations, only CSC coefficients away from spectral peaks are listed here. CSC is found between K_p (and to a lesser extent between Wolf's

number) and several of the neonatal indices in Moscow over 112 years at a frequency of one cycle in 7 years (P=0.004 for birth weight of boys; P=0.012 for body length at birth of boys; and P=0.007 for head circumference at birth of girls). This component had been singled out earlier as possibly being associated with cosmic influences (for review see Cornélissen et al., 1998). Moreover, the results of the transverse analyses carried out herein are in keeping with results obtained longitudinally with nearly 40 years of data (Sothern et al., 2005). Specifically, the blood pressure of a clinically healthy man was found to cross-correlate positively (P<0.05) with several planetary indices of magnetic activity peaking at a lag of 1 month while his heart rate cross-correlated negatively (P<0.05), the strongest association occurring at lag 0.

For heart rate, a statistically significant spectral coherence was also found at a frequency of one cycle in 0.493 year (P<0.001). Associations between geomagnetic disturbance and heart rate had been noted earlier (Cornélissen et al., 1996, 1999; Baevsky et al., 1997) and may have a bearing on the increased incidence of myocardial infarctions observed on the day following a southward turn of the vertical component of the interplanetary magnetic field's induction vector (Halberg et al., 1991; Cornélissen et al., 1994; Breus et al., 1995; Roederer, 1995). Geomagnetic disturbance indices are characterized by a prominent half-yearly component (Grafe 1958; Fraser-Smith 1972) that may account for infradian changes in circulating melatonin with a pattern that varies with latitude (Martikainen et al., 1985; Tarquini et al., 1997c). Using a linked cross-sectional (hybrid) approach, associations between the local geomagnetic disturbance index, K, in Moscow and neonatal heart rate and blood pressure have also been shown (Syutkina et al., 1997). These results involved components with a period of about 7 days, which are very prominent in the circulation of human babies and may have their counterpart in the fourth harmonic of the solar rotation (Halberg et al., 1991).

The foregoing time series analyses (time-microscopy) revealed that effects from the sun other than those mediated by visible light may differentially influence different body features of the same population of babies (De Rudder, 1952). The 10.5-year Schwabe cycle in sunspot numbers was reflected in the body weight of girls, but not in that of boys. Neonatal length and head circumference showed numerical equivalents of the 21-year Hale cycle in Moscow at 55°N geographic and 51°N geomagnetic latitude. Furthermore, comparing Russians and Kazakhs in the same geomagnetic and geographical location in Alma-Ata at 43°N geographic and 34°N geomagnetic latitude, additional differences are found. Body weight in Alma-Ata showed for Russians an about 17-year periodicity in both boys and girls, corresponding perhaps to the global solar activity cycle (Makarov and Sivaraman, 1989), whereas in Moscow a 10.3-year periodicity was found in girls-only. Kazakh girls and boys in Alma-Ata show a circavigintunennian period, which in boys is nearly double in amplitude, as compared to that of girls. By contrast with the differences in neonatal weight, the dynamics of body length are more similar at different latitudes, with a prominent about 20-year periodicity resolved by non-linear least-squares in data from each of the sites investigated (including Minnesota). Clearly, the about 10.5-year Schwabe cycle and the about 21-year double-polarity Hale cycle have numerical associations in neonatal biology as in adults (Halberg et al., 2006c).

The cycles in Nikityuk's data are the sum, or rather the product, of effects occurring both in our lifetimes and over the much longer spans of an external Darwinian (1859) as well as an internal

integrative evolution (Halberg et al., 1990). The question whether the rhythmic element of chronomes is endogenous or exogenous, a topic of debates in newspapers as well as at symposia, is ill-posed for any organism as an open system. The proposition of many Soviet investigators that earthly life is a contemporary echo of the sun pays homage to Pavlov while ignoring Mendel. The sun's photic and nonphotic effects eventually entered our genome and thus rendered us responsive to several latitude-dependent master-switches at selected frequencies. A scenario of our "adapting" to internal needs by temporal interactions within us as well as by adaptation to external stimuli is offered by the study of the ontogenies of humans, pigs, rats and crayfish in a broad phylogenetic perspective (Halberg et al., 1991; Cornélissen et al., 1999). Nikityuk's views are shared by those who find that the sun acts via space and terrestrial weather (De Rudder, 1952), via pandemics (Ertel, 1993; 1994; 1996), economics (droughts) and political upheavals (Mikulecky, 1993; 1994; 1997). Physiological associations are reinforced by morphologic effects upon newborns, noted elsewhere. At middle latitudes on earth, the primary synchronizing effects of visible light and temperature are reinforced, not confounded, by those of secondary synchronizers, in the last analysis also cosmic in origin (Tarquini et al., 1997c). We use herein the word "cosmic" advisedly by accepting the testability that there may be effects from beyond the solar system that bring about storms of the interplanetary magnetic field rather than the latter originating exclusively in the solar system. This would be an answer to the observation that a rise in systolic, mean and diastolic blood pressure may precede a magnetic storm in space, the latter gauged by a southward turn of the vertical component of the interplanetary magnetic field, Bz, an effect detected by superimposed epochs (Halberg et al., 1991).

17. Soldiers' stature mimicking Hale cycle in neonatal body length

The systematic patterns in human adult physical stature also shows associations with Wolf's relative sunspot numbers that broaden the history of physical stature in the context of the economic development (Clarke, 1838; Komlos, 1988; Halberg et al., 2003a). Long-term cycles in physical stature lasting several generations were noted by 1985 (Komlos, 1985). Woitek (2003) reported short-term height cycles that were similar to business cycles. Using spectral analysis techniques, the physical stature of Americans and Europeans in the 18th and 19th centuries was found to cycle with periods of about 7 to 10 years as well as with periods of about 3 to 5 years, as also reported for economic variables such as grain prices (Woitek 2003). An influence of economic cycles on physical stature may be particularly important in infancy (Komlos, 1985, 1998; Woitek, 2003). The association between height cycles and business cycles was reportedly weaker among the rich, and weaker among men than among women (Sunder and Woitek, 2004). The intensity of the relationship also seems to have declined over time (Sunder and Woitek, 2004). Low-frequency components have also been reported from height records of military

recruits in Sweden (Brabec, 2004), France (Komlos, 2003), the Habsburg Monarchy and 20th century Austria (Weber et al., 1998).

Against this background, data on body length recorded between 1670 and 1800 in six regions of Europe have been reanalyzed and summarized by Komlos et al. (2004). Multidecadal periodicities and cross-correlations with solar activity were noted with soldiers' height. The economist Hyde Clarke (1838) was the first to report an about 11-year economic cycle in print (cf. Schove, 1983), doing so in the same year when Schwabe (1838; see also Schwabe, 1844) published data clearly showing the cycle but refrained from writing about periodicity. Quite apart from a communality of cycles in biology and the environment, changes in solar activity have been associated with changes in the weather (Labitzke and Vanloon, 1993), which in turn may influence economic cycles (Kondratiev, 1935). The case has been made earlier that business cycles may bear on body weight and length (Komlos, 1985, 1998, 2003; Woitek, 2003; Brabec, 2004; Komlos et al., 2004; Sunder and Woitek, 2004). At birth some decisions concerning adult stature are already made, since the signature of the environment in terms of the about 21-year Hale bipolarity cycle of Wolf's relative sunspot numbers found in adult soldiers is an association also present at birth. A task for those concerned with short stature could become preventive if the sensitive stages when the environment may inhibit growth could be found, as well as means to shield from, compensate for or otherwise counter the undesirable effects of space weather.

Summary

Growth depends upon more than nutrition. Interacting, transdisciplinary cycles of greatly varying lengths, resolved with their uncertainties, as CIs, i.e., 95% confidence intervals of their parameters, characterize growth. Several non-photic cyclic effects exceed in amplitude, A, the A of the spectrally neighboring photic effects of the sun, such as circadian and circannual As. For this presentation in Florence (X International Congress ox Auxology), we report, with Latin keywords:

1. Some new physical environmental cycles, in the strict sense, given with CIs of their characteristics, beyond those found by physicists. There are more periods around us than recent treatises on astronomy and solar and cosmic physics visualize as characterizing our environment. **Novitas revolutionum physicorum.**
2. Many new transdisciplinary biospheric cycles (in the strict sense with CIs of their characteristics). **Novitas revolutionum biosphericorum.**
3. Similarity of biospheric and physical environmental cycles. Many periodicities in one field have counterparts in another field: thus, the periods of several biologic rhythms such as those of a week, and a near-transyear (longer than a calendar year by a few weeks) are found with overlapping CIs in geomagnetics, heliomagnetics, helioseismology and cosmic rays in the satellite-measured solar wind and, vice versa, the physicists' cycles are found in the biosphere, such as fartransyears (of 15 or 18 months). **Similitudo revolutionum physicorum et biosphericorum subsequently defined as congruence.**
4. Resonance. Periodicities in us can dampen when we do not detect their counterpart outside us and are amplified when the counterpart reappears outside us, a subtraction-replacement approach constituting a basis for postulating "resonance", quantifiable changes in the same direction of the amplitude, A, of the cycles involved. **De revolutionibus resonantibus.**
5. Pulling by environmental cycles. There can be similar temporal variations quantifiable by the phases of the cycles involved around and in us, whether contemporaneous or with a lag in us, after a change outside us, in keeping with a pull, if not drive. **De revolutionibus physicorum trahentibus.**
6. Partial endogenicity. The circadian rhythm as a component of photic origin is directly documented as genetically anchored; similarly, transyears and weeks in organisms are not obliterated, just damped, when environmental counterparts cannot be detected. It seems reasonable to assume an only partly exogenous and indeed partly genetically coded endogenous system for some or all non-photic as well as photic spectral components that we consistently encounter in the development of a species as well as in the development from the egg. **De revolutionibus resonantibus in biospheris ipsis.**
7. Ontogenetic and phylogenetic rhythm dating may look at living fossils, dating back much further than all currently available instruments of physics.

Organisms become tools of physics, like Humboldt's magnetic dip meters, "dipping" into a remote past. **De adsignando tempore rhythmis ontogeneticis vel phylogeneticis.**

All of the foregoing findings, available as maps in time, are a natural starting point to deal with the mechanisms of growth heretofore relegated to an unspecified secularity. The cycles' characteristics will have to underlie any rational investigation of the mechanisms involved and their manipulation may lead to a meaningful account of when resonance among cycles or a pull by one or more of them is bad, good or neutral and how these interactions among cycles can be used for an optimization of growth and of the habitat in this context. **De ALIQUOT revolutionibus quae resonant et trahent inter se; hae sunt orbium coelestium, terrestrium, biosphericorum.**

Conclusions

1. A plethora of peripheral circadian clock genes complements information on the long-known cell cycle that maps events in a cell, to replace the stages G_0, G_1 and G_2 where the Gs stand explicitly for Gaps in knowledge. This cell cycle awaits further intracellular mapping, here begun by one of us (GK) for a study of mechanisms involved in circadian oscillation, with the development of new therapies in mind. The circadian cell cycle also constitutes immediately useful information for an optimization of the timing of new and already available agents, such as GH. Many potentially useful drugs may be lost because they are tested at the wrong time. The facts that the same agent does or does not act, or even has opposite effects only as a function of circadian and other, e.g., circaseptan timing must not be ignored.
2. Far beyond the very important circadians and circannuals, associations of (nonphotic) space weather with growth accumulate at different levels of organization, ranging from physical stature to mitosis; it becomes mandatory that global monitoring on earth, services that were initiated in the 19th century by Humboldt, Gauss and Sabine in physics, and have continued ever since, also in space, be not only maintained but enlarged in scope and aligned in terms of density and continuity of sampling with a complementary systematic broad biological, including growth, monitoring. This endeavor to extend by far the lifetimes of individual investigators should become a government-supported undertaking in appropriately picked "test pilots" from womb to tomb, as a global monitoring endeavor now ongoing in physics.

"Ancestors" measuring trends in children's growth: a step toward cycles and the cosmos

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Trends, cycles and chaos make up variability in time, within and among individuals. They are usually measured in populations and trends most obvious in growth, were recorded first. Other effects, if recognized at all, were dubbed "secularity".

The beginning of the industrial age in Europe and in the United States during the second half of the 19th century brought riches to some but not to the common worker. Often children also were put to work in the factories. At that time, public health (and in particular also school) officials started to be concerned about the health and welfare of children. Many surveys in nurseries and schools were started for cross-sectional (transverse) and longitudinal as well as linked cross-sectional (hybrid) studies.

Adolphe Quetelet (1796-1874), mathematician and statistician, born in Gent, Belgium, established the still used body-mass index (BMI, weight (kg)/ height $(m)^2$ and tried to find measures for his average man ("homme moyen"). He persuaded the British Association for the Advancement of Science to establish a separate Statistical Society in London in 1834. He reportedly said: "Mundum numeri regunt" (numbers rule the world), in keeping with the citation from Pythagoras: "numbers model everything". Quetelet's French contemporary and friend, Louis Rene Villermé (1782-1863). introduced vital statistics seeking to establish the "True Law of Populations".

In England Francis Galton (1822-1911), a half-cousin to Charles Darwin, a leading British statistician, among his many other fields of scientific interest, pursued anthropological statistics in schools. Galton advocated anthropometry and eugenics; indeed he coined the terms. He also introduced the method of percentile grades. He favored selected parenthood to improve the human species; the frequently used quotation "nature and nurture" is traced to him, discussed in his book: "English Men of Science: Their Nature and Nurture", 1874. His studies on twins led to investigations on twins reared apart, demonstrating the heritability of circadian rhythms in human heart rate. Galton developed fingerprinting as a method for identification.

Gradually anthropometry -- as far as the study of the growth and development of children was concerned -- used the name auxology (auxometry), derived from the hormone auxine, from the Greek word "auxeine" (= to grow), a phytohormone,

chemically a tryptophan derivative, found in growing plants, a name more suitable to the subject. Charles Darwin was among the first to dabble in plant growth hormone research, writing a book on "The power of movement in plants".

Alfred Binet (1857-1911) spent "quality time" with his daughters, which led him to recognize individual differences in mental performances. With Theodore Simon he developed the Binet-Simon test to identify areas of weakness in school children, leading to the intelligence quotient (IQ) test relating the mental age to the chronological age.

T. Wingate Todd (1885-1938), professor of anatomy and anthropometrist at Western Reserve University (Cleveland, Ohio), published an Atlas of Skeletal Maturation (1937) and developed a "head spanner", an instrument to measure the diameter of the head.

In contrast to transverse studies, Luigi Pagliani in Turin, Italy, (1847-1932) introduced a longitudinal individualized complementary approach. Franz Boas (1858-1942) and Nancy Bailey (1899-1994) in the USA, and eventually James Tanner (b. 1920) in the UK, focused longitudinally on the "tempo of growth" assessed by growth charts.

Maria Montessori (1870-1952), born in Chiaravalle, in the province of Ancona, Italy, was the first female physician in Italy, graduating from medical school in Rome in 1896 with a score of 100 out of 105. She later studied psychology and philosophy. Her concern for children manifested itself early. She viewed mental deficiency as a partly pedagogical rather than only a medical problem. Children needed to be trained in schools rather than in hospital environments. She devoted her life perfecting education, developing an educational theory with methods that she found in medicine, education and anthropology and started a small school in Rome for challenged youth. Later she directed a system of daycare centers for working class children in one of Rome's worst neighborhoods. She is quoted as saying "I studied my children and they taught me to teach them". She approached the children from a paedagogical rather than anthropometrical viewpoint and her schools mushroomed all over the world.

Jean Piaget (1896-1980), born and educated in Switzerland, worked thereafter in France with Theodore Simon, the collaborator of Alfred Binet, as developmental psychologist with emphasis on reasoning. As a foundation of child psychology, he defined certain developmental stages of the infant and growing child up to the age of 12 years, when children are able to think about abstract relationships, understand methodology and can formulate hypotheses.

In the U.S.A. Arnold Gesell (1880-1961), born in Alma,Wisconsin, sought universal developmental norms during the first years of life for mental, motor, linguistic and social growth. Theodor Hellbrügge in Munich, Germany, deserves credit for introducing some rhythms into the systematic study of the child. He documented the development at different ages of the various 24-hour rhythms in

children, in the context of circadian systems. Still earlier, Bernhard de Rudder elaborated on many seasonal rhythms in populations of children in the context of a meteorobiology. Hellbrügge, using Montessori's teaching methods, recognized the opportunities of teaching children without disabilities and partly or fully handicapped children together so that they may help each other. In the footsteps of Maria Montessori he built the discipline of social pediatrics, again with institutes in many countries.

Many other "ancestors" also contributed a framework for the demonstration, first that there is a built-in structure in time in the morphology, physiology, psychology and pathology of children as well as in adults. Chronomics, the study of time structures, chronomes, derived from chronos-time and nomos-rule, led to the demonstration of the role of the cosmos in a number of new rhythms in body size and with respect to behavior, including autism. That rhythms are innate in part is the lesson of the second part of the 20th century. Moreover, the recognition that built in photic cycles such as those of a day and a year, are complemented by very many nonphotic ones, led to a budding chronoauxology. Its most important ancestor is Alexander von Humboldt, who in 1845, in his Kosmos (volume 1, page 340), defined climate broadly as "all changes in the atmosphere that influence our organs". Chronocosmoauxology extends his definition to all changes around us (from near and far) that occur now and took place in an evolutionary past, that influence our growth including our body size and much more. A microscopy in time shows that the element of cycles is coded in our genes for circadians as a start and for many other periods characteristic of growth, measured in hours or up to decades.

Addendum

While this paper was in press, Timothy Bromage et al. (2009) proposed: A hypothesized autonomic long-period rhythm controlling osteoblast proliferation and striae of Retzius repeat intervals agrees with data presented on mammalian osteocyte density. Thus we believe that a strong circumstantial case exists for central autonomic control of long-period rhythms over aspects of life history such as body mass. We term this hypothesized period the Havers-Halberg Oscillation, with reference to Clopton Havers [1691], the first to observe and describe both the lamellae in bone and the striae of Retzius in enamel, and Franz Halberg, a long-time explorer of long-period rhythms (Halberg et al., 1965, 2004)

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