

## Epistemological and Philosophical Bases of Chronobiology

Pietro CUGINI, Giuseppe D'ANDREA, Loredana Di PALMA, and Kohji TAMURA<sup>1)</sup>

*Endocrine Pathophysiology (Chronobiology Laboratories), University of Rome "La Sapienza" and <sup>1)</sup>Department of Medicine, Yamanashi Medical College*

**Abstract:** Since chronobiology and medicine is a new science, epistemological and physiological bases should be clearly established. A scientific concept is important so as to apply this basically well-developed science to clinical medicine. Non-random and periodic time sequential variables in biology have been studied to prove the existence of biologic clocks in biology in general. Recent advances in morning device computer development, not only in software but also in hardware, as applied to clinical medicine, have enabled us to apply this approach to clinical medicine as chronomedicine.

**Key words:** Epistemology, Philosophy, Chronobiology, Chronomedicine

Among chronobiologists there is much discussion on the epistemological niche of chronobiology, and there have been various dialectical views on the matter. If it would be inappropriate to say that there is divisiveness within the discipline, certainly there is a clear disparity of opinion. Chronobiology is defined differently by different authors. Two such definitions, however, exemplify the divergent trends of thought.

One states that chronobiology is the "branch of science which objectively investigates and quantifies the biologic time structure including the periodic manifestations of life"<sup>1)</sup>. The other defines it as "a new methodology in the studying of biologic temporal structures and vital periodic phenomena"<sup>2)</sup>.

### EPISTEMOLOGICAL POSITION

To establish which of these two positions more suitably defines chronobiology, a brief

disquisition on the meaning of the word science is in order. To this author, science is the heuristic (reality description) and eidetic (reality cognition) exploration of phenomena in their normal and abnormal expressions.

Epistemologically, scientific investigation can be conducted by the analytical (Cartesian) or systematic (Darwinian) method. The former conducts investigation by dissecting natural phenomena into elementary components for measurement, simulation and/or falsification; the latter explores natural phenomena in their complex wholeness. In the systematic approach, scientific findings are not based necessarily on measurement, but on observation: that is, on mere objective assessment of phenomena. In turn, analytical science measurement can be indeterministic (i.e. relativistic or Einsteinian), or deterministic (i.e. quantal or Planckian). In the analytical-indeterministic conception, the magnitude or dimension of variable(s) is not an entity existing "a priori" but one relative to the system that generates it, varying as a function of dynamic and co-univocal relations with time, space, mass, and energy (see further). In the

1) Tamaho, Nakakoma, Yamanashi 409-38, Japan

Received October 17, 1990

Accepted November 20, 1990

analytical-systematic conception, the magnitude or dimension of variable(s) does not vary, but is a “quantum” of mass, constant in both isochronous time and in isometric space.

A scientific system is dually constituted by a theoretical (logical/speculative) body and pragmatic (technical/operational) one. The theoretical component provides the conceptualization of principles, and the inherent philosophical and epistemological bases which give the system the status of doctrine. The pragmatic component presides over the development of applicational norms conferring upon the system the attribute of methodology. A science that fully complies with the semantic meaning of the term is thus a discipline which encompasses principles and appropriate methodologic procedures in the context of a systematic field of phenomenologic observation. More specifically, the science which exercises its principles and methods with a non-applicational intent is defined as basic science. The science which professes its doctrine and methodology by pursuing operative goals is defined as applied science.

The classification befitting chronobiology can be easily drawn. If we accept the definition of science given above, there is no doubt that chronobiology must be regarded as a scientific discipline in the broadest meaning of the term. To label it a methodology would be incomprehensive. Chronobiology claims the full attributes of science in that it presents a) a doctrinal body whose principles rest on exact philosophic-scientific bases; and b) a methodology disciplined by mathematical and statistical protocol. Furthermore, the systematic nature of the phenomena probed by chronobiology cannot be denied since biologic rhythms are a fundamental property of living matter. Chronobiology is thus a science, an analytical scientific discipline based on measurement and on not mere empirical observation; among the analytical sciences, chronobiology tends toward a relativistic position because it introduces time as a necessary property in the

dynamic biologic system, alongside space, mass, and energy. Time as the fourth dimension of living matter is accounted for as a punctual (i.e. instantaneous time), progressive (i.e. temporal duration), and recursive (i.e. periodic) variable, inextricably present in any normal or abnormal biologic observation. The philosophy of dynamic systems provides the premise of chronobiologic methodology. Instantaneous time and duration are the bases of numerical non-inferential procedures (i.e. macroscopic chronobiometry); the period substantiates analytical, influential methods (i.e. microscopic chronobiometry). The indeterministic scientific model of chronobiology poses as the epistemologic alternative to the purely quantal, deterministic systems of analytical science. It must be stressed, however, that chronobiology does not want to be an alternative science. Its epistemologic position holds that the biologic “quantum” cannot exist without the biologic “tempus”. A detemporalized quantum indeed would remove the historical sequence from the biologic event since “before” and “after” would lose the autocorrelation which characterizes them. In biology nothing occurs without a precedent. “*Natura non facit saltum*.” the evolution of natural events, including biologic ones, cannot be conceived, nor exist outside a “*consecutio temporum*.”

Finally, it is necessary to point out that chronobiology explores biologic matter in its “phyletic past” (i.e. paleochronobiology), and “ontogenetic present” (i.e. neochronobiology), through both basic and applied research. Chronobiology thus articulates its principles and methodology not only to gratify heuristic and eidetic pursuits (basic chronobiology), but also to fulfill pragmatic purposes (applied chronobiology). In this, it seeks to safeguard health/normalcy in the plant and animal kingdom. For this reason, we believe that chronobiology can be more suitably defined as the scientific discipline that studies periodic biologic events while aiming to understand their

laws and nature, describing and quantifying their structure, utilizing their properties, and correcting their abnormalities, in the attempt to promote individual health and the preservation of the species.

#### PHILOSOPHICAL-SCIENTIFIC PRINCIPLES

Ascribing to chronobiology a philosophical basis could seem, on the surface, audacious, if not outright hazardous, and as yet another infelicitous intrusion of the “non-scientific” upon the “scientific.” However, dismissing the philosophical question would shortchange chronobiology as scientific doctrine as well as underestimate the import of philosophy upon the genesis and evolution of Science. The dichotomy between philosophy and science is deeply felt today: mutual cautiousness and suspicion abound among scholars in both disciplines, and the threat of heresy looms over inquisitive “crossover” studies, as a “closed shop” mentality is widening the cultural gap between the humanities and the sciences in general. Some scientists tend to dismiss the history of ideas as quaint and futile. It is easier to pretend that science has developed in an timeless, unbiased, cultural vacuum. The time dimension can be equally disregarded in the microcosm of biologic phenomena as in the macrocosm of human experience, but such temporal dispensation limits the factual accuracy of the natural phenomena observed as well as the critical faculty of the observer, itself a part of such phenomena. The symbiosis of science and philosophy is yet readily transparent; many a scientific hypothesis has been advanced by a philosophical quest, and, in turn, many a philosophical postulation has matured in the course of scientific pursuits.

Chronobiology, beyond its pragmatic/investigative scope, has a set of tenets at its core which prompt and motivate its endeavor. Pivotal to chronobiology is the confutation of such an accepted concept as temporal stationarity. The origin of such a notion can be

traced back to metaphysics, having being introduced by Parmenides in his cosmic theory of a universe that is stationary in time and space. Disserting on Pamenidism in the computer era may appear contrived and unnecessary, as the Greek philosopher’s idea has long been disputed and relegated to the care of historians of philosophy. In reality, the thesis of Parmenidism has been repropounded time and again, under different labels, producing tangible effects in the history and epistemology of Science. It bears its influence, notably, in the concept of stability of the “milieu interieur” put forth by C. Bernard<sup>3)</sup>- the putative father of modern biology- as well as in C. Cannon’s law of homeostasis<sup>4)</sup> where the constancy of biologic matter is adduced as fundamental requisite of biodynamic systems. Chronobiologic teaching reprobrates the homeostatic vision of biologic matter insomuch as it heralds the principle of biologic invariability or invariance, which cannot be reconciled with the ontogenetic and phylogenetic evolution of living matter. Chronobiology, moreover, takes a dialectically opposed view, and, on the strength of its rational antithesis, can be summoned in as a new philosophy of “being and becoming”.

The philosophical/scientific pith of chronobiology can be laid down in principles (Table 1). Of paramount relevance is the concept of biologic instability, which exacts time as an essential and inalienable entity, qualifying and quantifying such instability. Time, hence, is a biologic dimension, that is, an obligatory property of biologic phenomena. One basic principle of chronobiology states that living matter and time constitute necessarily a co-univocal “sine qua non;” in the paradigm of time as a quantifiable dimension of dynamic biologic phenomena, the general principles of science are affirmed. Chronobiology advances the theory of temporal relativity in biologic events by providing the link between physics and biology. Einstein’s mechanics affirms the relativity of time in the dynamics of physical phenomena. Chronobiology’s mechanics

Table 1. Principles that substantiate chronobiology

---

Biologic Time Relativity (Time as an entity necessary and co-univocal of biologic processes)
Non-linearity of biologic events or biologic periodicity
Spatial-temporal rheology of biologic rhythms along the irreversible linear axis of physical time
Clinospectrometry of biologic rhythms as function of age
Central chrono-organization of oscillating biologic functions
Biologic adaptation of biologic rhythms via synchronization with environmental cycles
Central hierarchical organization of biologic pacemakers
Multinodal network control of oscillating biologic functions

---

affirms the same truth in the dynamic unfolding of biologic events. B. Russell emphasized that temporal events constitute the substance of the world, setting modern physics on the side of Heraclitus, and against Parmenides. Chronobiology wholly accepts, and makes its own, Heraclitus' "Panta Rei" and totally rejects the "Immutable Being" of Parmenides' eleatic legacy. It must be clear, however, that biologic relativity is not bound by a mere reposition of Heraclitus' perpetual flow in its monotonic linear model. It submits, instead, a meta-heraclitean reassessment of biologic becoming. Biological observation conducted within a "temporal window" has indeed clarified that the great majority of living events occur with a systematically repetitive dynamic according to a cyclic periodicity<sup>5)</sup>. Biologic events thus oscillate periodically in their temporal dynamics with a frequency of oscillation ranging from milliseconds to years. The biologic organism has oscillating features at all its functional levels. It ensues that the biologic event is, by its very nature, an undulating rhythmic event.

In another principle chronobiology, therefore, affirms the nonlinearity of biologic dynamics, coming close, if not juxtaposing I. Prigogine's vision of the physical universe: stationary time does not exist, it exists only in the dynamics of stable systems<sup>6)</sup>. Moreover, in asserting the non-equilibrium of biology, chronobiology is in agreement, again, with Prigogine, that "the systems farthest from equilibrium undergo a transformation to attain an

even higher degree of order than existed before instability set in". All this is logical. Far from its point of equilibrium a system can reach a potential which can be dissipated in appropriate energy to fulfill transformational and reconstititional requirements. In other words, a potential generates another potential, hence an entropic/syntropic alternation, an obligatory sequence of necessarily cyclic ups and downs, a non-linear periodicity that explains the self-generation and self-consumption of living matter as a function of time.

The salient point in the non-linear periodicity of living processes pertains to the so-called cyclization of time, which involves a closed-cycle non-linear system. Here chronobiologic progression would be of a circular type with time turning upon itself-progressively summing itself up, and digressively zeroing itself at every cycle. The cyclic time model has a capacity for metempsychosis making time appear re-traceable and re-livable. The circular model does not take into account "wear and tear," nor progression toward extinction/death. The temporal mechanics of biologic dynamics according to set rhythms is reconcilable with chronologic evolution of the living being. If we admit to an open-type system, than time, per se, is irreversible and thus a linear event, and cyclic oscillation, an anterograde chronological progression, and thus a spiral event.

Along the time axis, cyclic biologic becoming

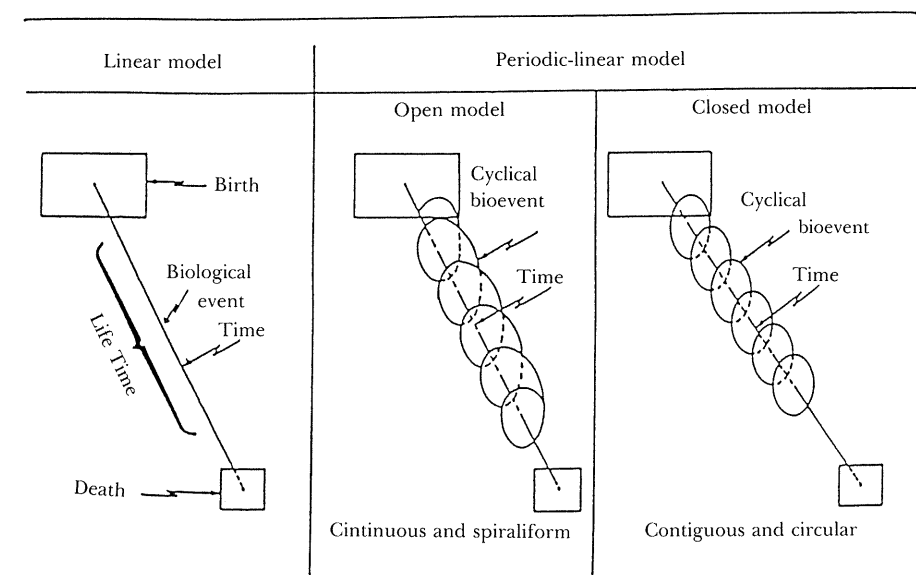


Fig. 1. Linear and periodic models of the aging process.

can be expressed by a helicoidal spiral (Fig. 1). In elliptic rotation, the beginning of a cycle entangles itself with the end of the previous one, and "before" and "after" assume a real historical progression. The spiraliform revolution indeed implies forwarding, directionality, and irreversibility of temporal/spatial advancement. In biologic cycles a temporal/spatial distance is thus covered. This period constitutes a duration in the existence of a living organism.

By conceiving of biologic rhythms as temporal-spatial rheologic events, and not as closed-loop circular phenomena, one can realize how existence is intimately related to bioperiodic repetitiveness.

In the rhythmicity of living functions, life has expressed its essence as instantaneity and flow. In this light, biologic rhythm acquires the dimension of a fundamental life unit, a metronome which concretely measures biologic dynamism in its ceaseless becoming. The attribution of a rheologic property to biologic rhythm yields the rheospectrometric concept of existence - another fundamental principle

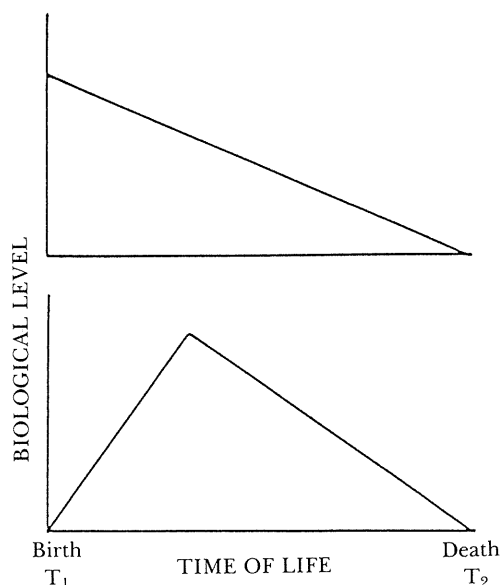


Fig. 2. Oversimplification of traditional models of aging.

of chronobiology (Table 1).

All forms of life in the animate world have a beginning and an end. Time modulates the rhythm of biologic existence, since life proces-

ses are a function of time. Traditionally, life is represented as a parabola along the time axis, or as a declining straight line (Fig. 2). In the latter case, senescence is regarded as a phenomenon beginning at birth; Anatole France writes "nous étions déjà si vieux quand nous sommes nés". Chronobiology joins with its own eidetic view of life/time: a spiral which encircles the time axis and whose spires express the periodicity of biologic events (Fig. 2). It must be taken into account, however, that with the increasing passing of time (i.e. years, decades) the rhythmic properties of many vital functions, though retaining their periodic features, undergo substantial change. Age-related rhythmic remodeling is currently designated as clinospectrometry (a neologism derived from the Greek *clinos*, meeting trend, and the measurement of spectrum wave frequency).

The chronoscopic variation in biologic rhythms can be illustrated in four patterns: 1. Change in the oscillating mean level (MESOR); 2. change in the extension of cyclic fluctuation (amplitude); 3. timing displacement of the sinusoidal oscillating crest (acrophase); and 4. change in periodicity.

From a heuristic point of view, age-related rhythmometric variations represent changes in both tonic and phasic activities, proper to the oscillating biologic function. MESOR clinospectrometry represents the decline of the tonic function, while that of the amplitude, the decline of the phasic function. It follows that the gerontological decline in phasic and tonic activity can be graphically represented by a progressive reduction in harmonic vibration (Fig. 2). However, it must be noted that in the chronobiologic description of evolution, physical time remains a linear function whose axis marks the seconds, minutes, hours, days, etc., of passing life. Time must be linear otherwise we would have to postulate that the angular velocity of light is greater than its linear velocity, in order to cover the longer circular space in the same time unit. Chronobiology underscores, therefore, the irreversibility

of the temporal moment, in antithesis with the concept of cyclic time which is proper to Eastern philosophy.

If throughout the history of human thought, physical time has been widely theorized about, albeit often, out of its immanent construct, traditional abstract/metaphysical speculations on the matter come to an abrupt end as Newtonian mechanics and Kantian philosophy instantiate physical time as a priori quantifiable datum. Biologic time has received less cognitant attention than physical time: theories have been more timid, and remain pervaded by incogrous transcendental/religious overtones, straying from scientific/rational thought. Epistemology, aware of this problem, currently attempts to overcome the excessive conventionalism of "empirical criticism". Purposely trying to settle the sharp controversy between relativistic and deterministic positions, epistemologist V. Tonin examines the validity of the irreversibility of temporal action within a broad context of biologic evolutionary capacity-intended as the capacity for successive and progressive levels of variation<sup>7)</sup>. For Tonini, evolution is not a mere process of homeostatic and ecological adaptation, but an informational process - a non-linear function of all preceeding history converging on a given biologic forum.

Left, hence, is an alternating of mutually overlapping entropic and syntropic processes. Only chronobiology, it appears, extricates biologic time from physical time: chronobiology indeed regards organismic time as a temporal biologic structure, a property of the ceaseless dynamics of life. The geroclinospectrometry (or gerospectroclina) of biologic functions represents another tenet of chronobiology. P. Engel remarks, "Life is woven of the warp and woof of space and time"<sup>8)</sup>.

The rhythmic course of biologic events perfectly explains the space-time symbiosis. Indeed, biologic rhythm is an isometric system in isotropic space. The rheologic property of

biologic rhythms reiterating the irreversibility of temporal action solves, thus, the longstanding antinomies of being and becoming, state and motion, position and velocity, instantaneity and duration, moment and flow, etc. In the unstable "milieu interieur" of living matter, biologic rhythm, moreover, offers objective parameters for living phenomena, hence applying the working definition of the scientific method. Biologic rhythm, as *gnome* (from the Greek unit of knowledge), does away with empirical evaluations by putting forth isochronous bioperiodicity as a medium to analyze the dynamics of living phenomena. In reiterating the temporal-spatial property of cyclic events, it behooves us to mention A. B. Kristofferson's "real-time criterion theory" which postulates that cyclic biologic phenomenon is nothing other than a time quantum<sup>9,10</sup>.

Kristofferson applies the concepts of quantum mechanics to biology, joining in this enterprise W. Weisenberg, an outstanding thinker in the development of quantum theory. Writing to Neils Bohr, Eisenberg remarks "perhaps the wealth of mathematical forms hidden in quantum mechanics is large enough to embrace biologic forms". According to Kristoferson's theory, the "cyclic biologic qantum" has a temporal magnitude on the order of milliseconds. Such a minimum temporal biologic quantum constitutes the elementary unit of time duration discrimination based on which the living organisms of phyletically higher order have cognizance and certainty of time.

Biologic rhythm as basic time quantum, hence complements not only physical and biologic time, but also psychological time. In the diatribe between relativistic and quantal mechanics, chronobiology is clearly more consistent with Einstein than with Max Planck. Among the reasons for this is that subjective time consciousness does not necessarily involve a quantal step. As early as 1780 Guyau held that the inner sensation of passing time depends on a duration estimate<sup>11</sup>, based not only

on quantitative but also on qualitative attributes of dynamic events (Table 2). Time sensing mechanisms may thus be indeterministic, based on temporal order discrimination, that is, on the temporal integration of the rhythmic sequence of movement. The perception of time resembles in some ways the perception of movement. J.J. Gibson states "events can be perceived but not time"<sup>12</sup>. If time were a physical entity unto itself, it would have to exhibit an univocal independent identity, measurable and freely perceived on its own grounds without need to resort to a frame of comparison external to the dynamic system. In fact, time can only be perceived and measured from outside of the dynamic system: externally observing motion or the change in the state of the system with respect to one or more fixed or motionless reference points. Relativistic mechanics corroborates such observation by demonstrating that inside a system in motion, temporal lengthening or expansion - which time is subject to on account of velocity - is not perceived.

Experiments performed on subjects totally isolated from the environment have yielded much concurring data: cognition of geophysical time is lost, notwithstanding internal reference parameters such as time intervals of physiological events (awake - sleep cycle, diuresis intervals, cardiac rhythm, etc.). At this point it is fitting to ask if time is not an abstract entity necessary to the cognitive system, that is, convenient for defining, comparing, and measuring events that undergo change of state or of place. Time is the logical by-product of dynamics. From outside a system in transformation it is impossible to conceive of time. As stated earlier, current chronobiologic thinking is purposely relativistic in its approach, and is little inclined to accept the quantum hypothesis of living matter's sequential rhythms, not wanting to admit a "time base", or a changeless and unvariable entity which subtly would revive, once again, Parmenides' "immutability".

Table 2. Guyau's subjective time-judgement determining factors

---

Intensity of given events
Intensity grading in the difference among events
Numerical quantity of events and numerical quantification of their differences
Number of successions per unit time of given events
Relationship among events: their intensity, similarities, differences, and position in time
Time necessary to conceive of events and their interrelation
Level of attention span required by the events and the sensation of pleasure or fatigue which accompanies them
Specific emotions solicited by the events
Our attitudes toward and expectations from given events

---

The time quantum presupposes, among other things, an interquantal latency, another changeless entity representing the *ouden* (from Greek non-being), the non-entity, a kind of non-time or time-pause. In the quantal view of biology, becoming becomes discontinuous, due to contiguity, as in a binary digital flow. Once again, this is contrary to the axiom "*Natura non facit saltum*", which succinctly affirms a continuous and analogic becoming in the temporal unfolding of biologic functions. Not only in physics but also in biology there is thus an antagonism between the indeterministic and deterministic propositions of dynamic processes. For chronobiology's relativistic thesis, periodic properties, and thus analogic ones, imply instead the necessary existence of a clock, as an entity which changes with time, according to an order judgement (which of two events appears first in a series).

The control of biologic time by internal clocks gives rise to an additional principle of chronobiology (Table 1). The existence of a biologic clock is not only a practical/functional requirement, but also a theoretical/logical one. In relativistic physics, the relation among several dynamic events is specified in Einsteinian terms of simultaneity and succession. Repetitiveness or recurrence is a property of physical-mainly geophysical - time, visibly ascertainable in the alternation of days and seasons, which presupposes an entity capable

ing (information gathering) and of remembering the previous occurrence of a given event. Thus, in order to perceive and measure physical time, a timing device external to the intrinsic property of time - a clock - is required. In relativistic biology, that is, in chronobiology, the simultaneity succession and repetitiveness of vital events are cogently stressed. The biologic clock is logically and functionally necessary. To discriminate time something that mimics temporal flow must exist in all living systems. The term "internal clock", coined in 1933 by Hoagland<sup>13)</sup>, records the passing of time in the fashion of a tape recorder's "counter". In the economy of living matter these devices are essential cognitive instruments in the fulfillment of vital functions, as they provide a "temporal horizon" as a reference for temporal self-regulation and for self-consciousness. The trinomial set of simultaneity, succession, and repetitiveness probe the quality of physical time. The rheologic principle of biologic rhythm proposes, instead, other properties as specific time attributes of living organisms. In the periodicity of biologic events, the capacity of living matter to regenerate its morphology and structure according to a timely agenda must be considered. The biologic clock has the capacity to program living matter to self-sustaining, functional self-organization. Self-organization implicates, in turn, the processing and memorization of data



in the vital substrate. The epistemologic magnitude of this concept is awesome; not surprisingly it elicits enthusiastic consensus among contemporary thinkers. V. Tonini holds that "both phylogenetic and ontogenetic biologic dynamics are grounded on memory equipped informational systems. Accordingly, the evolution of a given biologic configuration at a given moment occurs as a non-linear function of alternating entropic/syntropic processes which were mutually imbricated and ensued one another according the alternating rhythms"<sup>14)</sup>. The self-preservation property of living matter, which materialize in the periodic course of biologic rhythm, represents, thus, a programmed interchange of vital energy. In this view, biologic clocks take on the function of timers, conferring a rhythmic cadence to biologic events.

Drawing again on physics, biologic clocks have been variously referred to as "biologic time donors", "oscillators", "pacemakers" or in C. Pittendrigh's rendition, automatic pulse generating mechanisms that self-sustain oscillation<sup>15)</sup>. The biologic pacemaker is, hence, the programming elementary unit of life in that it chrono-organizes the functioning of living matter. One must, however, necessarily accept that the ability for cyclic temporal programming exists in genetic heredity in addition to the capacity for cloning substance and function. I. Prigogine and I. Steingers admit that self-organization is the key to life. "We are tempted to go so far as to say, that once the conditions for self-organization are satisfied, life becomes as predictable as the Bénard instability of a falling stone". A principle of Chronobiology expounds such a thesis proposing chrono-organization as essential to biologic material (Table 1). The naturalistic analysis of the biologic world clarifies how living organisms interact with an ever-changing environment. Survivability exacts the internalization of change. A biologic clock that chrono-programs vital functions must, then, display adaptational skills and be interfaced

with the external and internal environment. The clock's bipolar interfacing explains the adaptability of biologic temporal programming toward environmental conditions acting in periodic succession (namely, light-darkness alternance, seasons, occupational rhythms, etc.) and therefore termed entraining agents<sup>15)</sup>, or *Zeitgeber*s<sup>16)</sup> (from the German time/donors) or synchronizers<sup>1)</sup>. The adaptive capacity of biologic clocks has been demonstrated by experiments performed on individuals living in total isolation, cognitively time shielded. These subjects, besides failing to estimate physical time, exhibit free-running cycles in place of circadian ones. The biologic clock, by recording external stimuli and programming internal events, coordinates, in unison, biologic and physical time, contributing to the adaptability of living-matter chrono-organization. It is not our purpose to describe the mechanics of biologic clocks. It is instead germane to our aim to illustrate their functional role and their location.

A principle of chronobiology pertains, in fact, to the hierarchical disposition of biologic pacemakers. It was stated earlier that biologic rhythms are present in all forms of living organization. In eukaryotic organisms, from the unicellular ones to man, the site of pacemakers is, thus, ubiquitous. Any living system presents two fundamental aspects: 1. coordination of multiple oscillating biologic processes; 2. central organization of their behavior. For the accomplishment of these functions, a central control is necessary, a sort of government, as it were, that organizes and synchronizes the multitude of peripheral biologic clock units. Left to its own devices, each biologic clock would confer a "free-running" rhythm to the organism, enacting in the general economy of life the "whole within the whole" axiom of Anaxagoras' philosophy. The hylozoic panvitalism inherent in such a concept does not, in practice, translate well into physical coordination among parts. Unitarian functionalism is ill-suited for the biologic complexity of plur-

icellular organisms of higher phyletic order. Chronobiologic research has otherwise clarified that the bio-periodic functional arrangement is insured by biologic clocks placed in hierachical order with ever-increasing apical command competencies in the molecular, tissue, organic, and organismic configuration. Such a vertical structure admits the centrality of governance, a "central drive" collectively represented by primary biologic clocks which set in unison the innumerable peripheral pacemakers charged with ever more regional time-monitoring responsibility. The biologic clock that centrally harmonizes biologic time may be considered an iterative device which carries out the function of Anaxagoras' Nous: that is, of a central intellect. Says Aschoff, "there is ample evidence that the clock represents a multioscillatory system which comprises driving (self-sustaining) and drive (self-sustaining as well as damped) units"<sup>17</sup>). The primary oscillator may thus be considered a center which weaves together functions of separate areas according to a precisely conceived rhythmic programme. Considering these features, the central pacemaker can only reside in non-mitotic tissue. The logical locus of central pacemakers is the post-mitotic tissue of the central nervous system, especially the hypothalamus in mammals, and the pineal gland in birds and lower vertebrates. The pacemaker could be regarded, at first, as a kind of Talete's arche, "the genesis of all time". This in reality is not the case. The biologic clock is a post-natal structure, incapable in itself of initiating a rhythm. Rather, it coordinates a program prompted at the genetic level. The central coordination of cyclic vital functions introduces the principle of chronobiology which overrides the axial system vision of biologic function.

Chronobiology contests biologic functions that cybernation conceives as simple "feed-forward" and "feed-back" mechanisms. Biologic communication traffic between command centers and outpost stations cannot but be

based on network-type pathways, as in an interactive integrated multisystem in which data reciprocally circulates via "lateral" mechanisms otherwise known as "feed-sideward mechanisms"<sup>18,19</sup>). From this correlational network derives the "central" chronomodulation which renders life a eurhythmic course of cyclic biologic events.

#### REFERENCES

- 1) Halberg F, Carandente F, Cornellissen G, Katinas GS. Glossary of Chronobiology. *Chronobiologia* 1977; **4**(Suppl. 1): 1-189.
- 2) Tarquini B. *Chronobiologia*. In: *Patologia medica*, vol. 2. Piccin Editore, Padova, 1981: 2587-2601.
- 3) Bernard C. *Introduction a l' Etude de la Medicine Experimentale*. Paris, Lafume, 1824.
- 4) Cannon WB. Organization of physiologic homeostasis. *Physiol Rev* 1929; **9**: 399-431.
- 5) Halberg F. Temporal coordination of physiologic function. In: *Proceedings of Cold Spring Harbor Symp. Quant. Biol. - Long Island Biol. Assoc. N.Y.*, 25-289, 310, 1960.
- 6) Prigogine I. *La Thermodynamique de la Vie*. Recherche 1972; **3**: 547-562.
- 7) Tonini V. *La Vita e la Ragione*. Bulzoni, Roma, 1973: 1-153.
- 8) Engel P. *Companion guides to the universe*. The Sciences 1984; **4**: 51-54.
- 9) Kristofferson AB. A real time criterion of duration discrimination. *Percept. Psychophys* 1977; **21**: 105-107.
- 10) Kristofferson AB. Quantal and deterministic timing in human duration discrimination. In: Gibbon J, Allan L eds. *Timing and Perception*. Ann. N.Y. Acad. Sci., 1984: 423: 3-15.
- 11) Guyau M. *La Genèse de l' Idée de Temps*. Alcan, Paris, 1890.
- 12) Gibson JJ. *The ecological approach to visual perception*. Houghton Mifflin, Boston, MA, 1979.
- 13) Hoagland H. The physiological control of judgement of duration. Evidence for a chemical clock. *J Gen Psychol* 1933; **9**: 267-298.
- 14) Tonini V. Il testamento scientifico di Einstein. In: *Tempo Fisico e Tempo Umano*. La Nuova Critica 50-51, 5-83, 1079.
- 15) Pittendrigh CS. Circadian rhythms and the circadian organization of living systems. In: *Proceedings of Cold Spring Harbor Symp. Quant. Biol. Long Island Biol. Assoc. N.Y.*,

- 1960; 25: 159–182.
- 16) Aschoff J. Zeitgeber Der Tiorischen Tegesperiodik. *Naturwissenschaften* 1954; **41**: 49–56.
- 17) Aschoff J. Circadian timing. *In*: Gibbon J, Allan L eds. *Timing and Time Perception*. Ann N.Y. Acad. Sci. 1984; 423: 442–468.
- 18) Sanchez de la Penas S, Halberg F, Ungar F. Pineal chronomodulation. *The Feedsideward*. Clin Chem Newsletter 1982; **2**: 129–130.
- 19) Sanchez de la Penas S, Halberg F, Halberg E, Ungar F, Cornelissen G, Sanchez E, Brown G, Scheving LE, Yums EG, Vecsei P. Pineal modulation of ACTH 1–17 effect upon murine corticosterone production. *Brain Res Bull* 1983; **11**: 117–125.