CHRONOBIOLOGY IN A MOON-BASED CHEMICAL ANALYSIS AND PHYSIOLOGIC MONITORING LABORATORY

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ABSTRACT

Biomedical science and astronaut health are both served by a telehygiene system[1] in space. It is to monitor blood pressure, heart rate and other body functions; it is also to interpret, for risk assessment, a spectrum of *intermodulating* ultradian-to-infradian rhythms and trends with age. This time structure, the chronome, consists, along with circadians, of about 3.5-day and about-7-day variations, the circasemiseptans and circaseptans, respectively. The latter characterize cardiovascular and other pathology. Chronobiologic assessment of elevation in the risk of developing cardiovascular, emotional and other disease is desirable for missions in space. Lunar along with terrestrial physiologic monitoring under conditions reproducing on-earth schedules considered and optimized for a stay on the moon and also for space flights yields also basic information by comparisons of concomitant and sequential in-space-flight, lunar and terrestrial records. Space flights add control data on any effect upon the chronome of microgravity and/or of removal from cycles in geomagnetism, as gauged by the blood pressure and heart rate chronome. As the moon turns, it permanently shows the same face to the earth; cycles related to earth-moon interactions (the large gravitational pulls leading to the tides) are not felt on the moon, where it can be examined whether rhythms

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[1]A computerized health care system, to be developed, operating at a distance from medical facilities, for two complementary purposes: 1) timely and timed treatment, screening, diagnosis and prognosis—the tele<u>medicine</u> part of the system. By initial focus on the automatic collection and interpretation of blood pressure and heart rate data, the prototype system serves cardiovascular telemedicine. The name 'tele<u>hygiene</u>' (from *hygies* = health) implies the additional task of health improvement by risk detection and risk lowering. Thus, the recognition of a circadian amplitude increase prompts treatment for risk lowering before there is an elevation of the rhythm-adjusted mean. Cases of circadian amplitude-hypertension are thus treated to prevent any MESOR-hypertension (Halberg et al., 1988, 1990a).

are influenced, though not necessarily synchronized, by physical cycles associated with geomagnetism, gravitational attraction or other effects of the moon and solar winds for life on earth.

1. INTRODUCTION

1.1. BEYOND ADVENTURE

In the early days of human ventures into space, exploration took precedence over bioscience. John F. Kennedy wanted the U.S. to reach the moon. His wish was fulfilled, but the opportunity to monitor human physiology over long spans, before, during and after space flight, was not seized, nor was it exploited in the long flights of cosmonauts. As another US president favors returning to the moon, from there to proceed to Mars, and as US-USSR cooperation is intensified, it is worthwhile to prepare for a chronobiologic clinical-chemical and physiologic work station in space, particularly on the moon, by establishing the reference data for the given individual before as well as during and after a journey in space. Integrated facilities for lunar and terrestrial multivariable human (and murine) physiologic monitoring can provide practically useful as well as theoretically invaluable data on the chronome, in the context of three-way intermodulations among the organism's physiology, society, and the putative physical influences of the sun-moon-earth setting (Halberg et al., in press).

2. MOON

The moon exerts some extremely weak gravitational effects. As it slowly rotates, its exposure to the sun exhibits an average periodicity of about 29 days, 12 hours and 44 minutes. This long 'day' produces a very large superficial temperature variation which, despite the very low thermal conductivity of the lunar surface, must induce tensions and possibly cause, in this body without known tectonic plates, the moon quakes observed during the Apollo missions. The radiative effects of the lunar day will be the most likely periodical phenomenon to be felt by biological specimens on or near the lunar surface. Another effect which is not negligible, especially during the lunar night, relates to the illumination phases of the earth, as seen from the side of the moon facing the earth. The earth disk will be seen as about 13.5 times larger than is the disk of the moon seen from an observer on earth. The terrestrial illumination periodicity seen from the moon is like that of the cycle of exposure to the sun while on the moon, but the relative phases vary with the positions on the earth-facing side of the moon. The periodicity associated with the rotation of the earth relative to the moon has a frequency of about one cycle in 24 hours and 50 minutes. At this time, one can only conjecture as to its having a measurable effect. In view of these considerations, it appears highly desirable to conduct identical experiments in a laboratory on the far side of the moon, or at least at the rim of a crater where the earth is never seen and simultaneously at a station in full view of the earth disk.

3. SUN

Breus (et al., 1989 and in press) have suggested an influence by solar wind-generated physical cycles from sun-earth interactions on human myocardial infarction and other pathology. Effects on chronome components such as those shown in Fig. 1 may be associated with physical cycles from the gravitational attraction for the earth or with electromagnetic and related effects, exerted by the moon and/or sun. (continued p. 5)

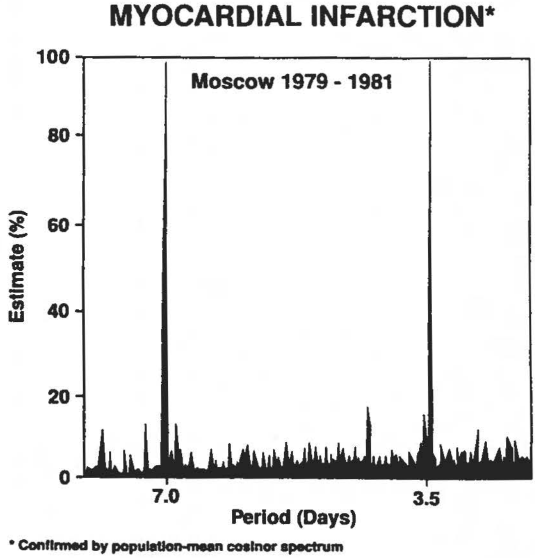
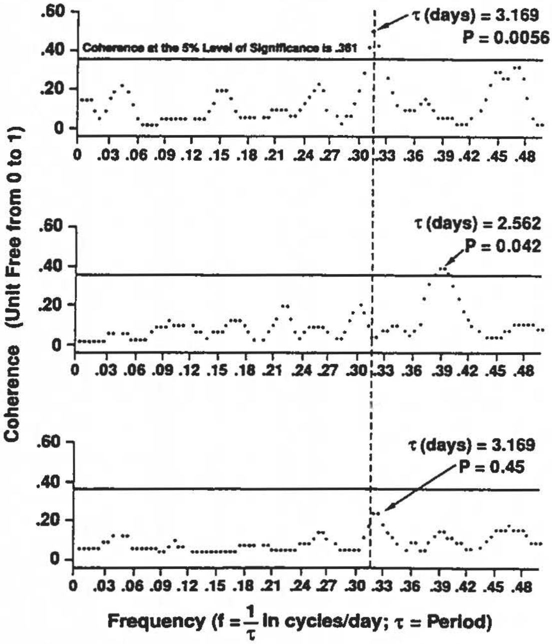


Figure 1. An about-3.5-day and about-7-day periodicity is revealed in an analysis (above) based on 85,707 telephone calls for an ambulance, leading in the hospital to the diagnosis of myocardial infarction (published by Breus et al., 1989). Similar results on strokes and other pathologies, based on over 6,303,860 calls accumulated over 3 years, are available (Breus et al., 1989 and in press). As compared to artifacts (such as a different rigor in *reporting* events during weekdays vs. weekends, or the inattentive *recording* of the calls during weekends), the *routine of living*, seems more likely to have an effect, albeit not a direct one. Societal routines may synchronize a partly endogenous rhythm, the latter documented by free-running, single stimulus induction, and a host of other *in vitro* and *in vivo* evidence (Halberg, 1980; Halberg et al., 1965, in press; Hildebrandt and Geyer, 1984). Global geomagnetic ('K') indices also exhibit a circaseptan periodicity during the same span and may influence the societally synchronized built-in circaseptan aspect of the human chronome, Fig. 2, as a socio-ecologic feedsideward (Halberg, 1983).

Figure 2 (next page). A cross-spectral coherence peak with a period of about 3.1 days is found between myocardial infarction and a global (K) index of geomagnetic activity during 2 of 3 years. There is no correction for multiple testing, albeit only the approximate, not the exact location of the coherence peak was predicted, and the peak in coherence is slightly away from the major peaks in spectra of myocardial infarctions and K indices, reasons for caution. In the experience of one of us (TKB), solar winds, via changes in the direction of the vertical (Bz) component of the interplanetary magnetic field, trigger diverse human pathology; if they did so predictably, they could represent the proverbial straw influencing, in a predictable insofar as rhythmic fashion (rather than randomly 'triggering') myocardial infarctions (Fig. 1), strokes, epilepsy, asthma, automobile accidents, street trauma

CROSS-SPECTRAL COHERENCE* DURING 3 CONSECUTIVE YEARS BETWEEN MYOCARDIAL INFARCTIONS AND A GEOMAGNETIC INDEX (K)



* Note coherence peaklet in similar spectral location in 1979 and 1981 (3.5 days = 0.286 cycles/day)

and a host of other conditions (Breus et al., 1989 and in press). By placing humans or rats on the moon, it is possible, at predictable times, to largely escape those effects of solar winds that are mediated by the earth's magnetosphere. Variations on earth are of the order of 5 x 10^{-3} Gauss, around a measured 'steady state' field varying from .3 to .6 Gauss. Exposure on the moon is mostly of the order of 10^{-5} Gauss, except for a fraction of a lunar cycle when the moon is in the earth's magnetotail, when it is about 10^{-4} Gauss. If, at these very low exposures, some effect should occur, the intermittent return and departure of the moon from the earth's magnetotail may be an advantage to the experimental design; the much-attenuated effect, with a difference in exposure between about 10^{-4} and 10^{-5} Gauss (as the moon enters and leaves the magnetotail, respectively), would provide a gradation of effects from what they are on earth, with its magnetosphere, as one extreme, to what they are when the moon is away from the earth's magnetotail, as the other extreme and with some very low yet intermediate exposure effects when the moon is in the magnetotail. If blood pressure were a sensitive marker rhythm for such effects (Easterly, 1982), it should be automatically monitored during space flight on each crew member by the use of unobtrusive instrumentation. This part of a personalized telehygiene system would serve the astronaut's health care in any event. This is its *raison d'être*. The same system, however, would also provide graded information of basic interest, as the crew is exposed to the alternation at a fixed lunar location in and out of the magnetotail of the earth during consecutive fractions of a lunar cycle. The results would also relate to a repeatedly considered relation of geomagnetism to emotional behavior (Friedman et al., 1963, 1965).

(continued from p. 2)
Solar wind, by the velocity and density of its plasma flow, brings about variations in the geomagnetic field, notably in the earth's magnetosphere. This solar wind-magnetosphere interaction constitutes a magneto-hydrodynamic generator which produces large-scale electrical currents in the magnetosphere. Thus, electric currents in the earth's environment are strongly associated with conditions in interplanetary space, as revealed by *in situ* measurement from rockets, balloons and earth-based magnetic field measurements as well as from satellites (that led to the discovery of the Van Allen belts).

The earth's magnetic field is commonly represented as the undistorted dipole-like field of a magnetic rod, with field lines extending infinitely. The solar wind, a continuous albeit variable stream of charged particles (mainly protons and electrons) emitted by the solar corona, confines the geomagnetic field into an elongated cavity called the magnetosphere. In the sunward direction, the solar wind compresses the geomagnetic field (bow shock), while on the night side the field is stretched downstream to form a very long magnetotail (more than 1,000 earth radii in length). The interaction of the solar plasma with the geomagnetic field is described by the Lorentz force: the force acting upon a charged particle is proportional to the magnetic induction $\bar{B}$ and to the component of the particle's velocity perpendicular to the field $\bar{B}$ and is directed at a right angle to both: a charged particle will spiral around a field line. The presence of an electric field perpendicular to the magnetic induction $\bar{B}$ will induce a motion of drift perpendicular to the direction of the fields. Particles with high-enough energy to penetrate the magnetospheric cavity are trapped along the lines of the geomagnetic field and become part of the radiation belts (Van Allen belts).

Because of the extreme plasma fluidity, a very complicated and very dynamic situation arises. When a flow of neutral plasma encounters a magnetic field, electrons and protons are deflected in opposite directions. This generates an electric current which induces its own magnetic field modifying the configuration and strength of the original magnetic field. The new magnetic field reshapes the plasma flow. This magnetohydrodynamic generator thus creates large-scale electric currents (polar current systems, magnetotail ring currents, etc.) (Fälthammar, 1973) that further disturb the configuration of the geomagnetic field.

Another source of geomagnetic perturbations has been linked to the influence of the lunar tides on the neutral earth atmosphere. The gravitational attraction of the moon modulates with a periodicity of a half lunar day the conductivity of a good conducting layer found at an altitude of (around) 110 km from earth, called the atmospheric dynamo. This lunar influence depends in a very complicated way upon the configuration of the sun-earth-moon system and has been known as early as 1835 (Chapman and Bartels, 1962).

The interplanetary magnetic field (IMF) $\bar{B}$ vector (magnetic induction vector) can be presented in the coordinate system of the solar ecliptic by three components, Bx, By and Bz components. Bz, the vertical component, is directed to the north polar ecliptic. The importance of the IMF Bz component for geomagnetic activity has been proposed by one of us (TKB), who postulates that a southward direction of Bz (Bz<0) 'switches on' the aurora in the earth's upper atmosphere and triggers substorms and storms in the magnetosphere, while the northward direction (Bz>0) 'switches off' these storms. The southward-turning Bz and its connection to substorms is described by Arnoldy (1971) and a pertinent sector structure by Wilcox (1968) and Wilcox and Ness (1965). The stronger the southward Bz, the stronger the geomagnetic field disturbance and the stronger the electric field and currents in the magnetosphere. When Bz abruptly turns from Bz>0 to Bz<0, total current in the magnetosphere increases up to 10 times within 5 to 10 minutes. Concurrently, a drop in potential across the earth's polar cap increases from 10 to 100 kilovolts.

An abruptly changing field as well as current generates electromagnetic waves in a wide range of frequencies from 1 Hz to 1 KHz. Variations in field orientation generate variations in atmospheric electricity and changes in the currents of the ionosphere, resulting in infrasonic waves. With these effects in mind, the frequency structure of the sunspot number and of the empirical K index (Bartels, 1957) were studied (Breus et al., 1989). The K index on hand is the maximal amplitude of variation in magnetic field strength during 3-hourly spans, estimated by a semiquantitative 10-point system. These estimations are carried out in and pooled from diverse magnetic observatories at different sites on earth. The average K index then characterizes global geomagnetic disturbance. Several sets of analyses by continuous spectra and by cosinor methods, with coherence illustrated in Fig. 2, thus far support but do not prove a possible relation of geomagnetism and myocardial infarction. This is in keeping with Malin and Srivistava (1979), and at variance with Lipa et al. (1976) and Knox et al. (1979). That, as Fig. 2 shows, such effects are transients, depending on solar activity changes as these affect the earth's magnetosphere, can be examined *par excellence* on the moon.

Longitudinal records of variables such as blood pressure and heart rate, being mapped from womb to tomb as sensitive and important features of the cardiovascular chronome (Halberg and Cornélissen, 1991; Halberg et al., 1988, 1990b), are desirable to examine any lunar-solar effects, while developing cardiovascular aspects of an applied telehygiene system. Such records should cover years or at least months, particularly on candidates for space flight under conditions simulated to reproduce schedules in space, notably on the moon. The opportunities offered by a substantial reduction, during a stay on the moon, of the mechanical cycles related to earth-moon interactions should also be exploited and may constitute an aspect superimposed on any effect of the absence of geomagnetism or of microgravity as such.

Large perturbations of the geomagnetic field or magnetic storms which last for days are caused by increases in intensity of the solar wind due to solar flares. Shorter term variations (of about an hour's duration), the substorms, are believed to originate in the magnetotail when two plasma sheets of opposite magnetic polarity merge (magnetic reconnection). This sudden collapse of the magnetic field showers high energy electrons on the earth's polar caps and generates the spectacular auroras. The substorms occur simultaneously on both hemispheres (Hones, 1986).

4. HEALTH CARE DURING TRAVEL IN SPACE AND ON SPACE STATIONS

That the about-24-hour (circadian) periodicity of human heart rate persists during space travel was demonstrated with the cosinor method over two decades ago (Halberg et al., 1970). Many subsequent studies relied mostly on the inspection of the data by the naked eye rather than on chronobiometry. With this qualification, internal dissociations of circadian rhythms and sleep disturbance under highly demanding operational conditions have been reported in the simulated Skylab mission (Wegmann et al., 1980a and b; Winget et al., 1984) and during actual flight (Dietlein and Judy, 1966; Dietlein, 1977; Nicogossian, 1977; Vasquez et al., 1987). Problems considered earlier include the individual's and the group's psychophysiologic and cardiovascular performance (Nicogossian et al., 1976; Egorov, 1980; Charles and Bungo, 1986), eye movements (Quadens and De Lee, 1974; Quadens and Green, 1984), the underlying neuroendocrines (Leach and Campbell, 1974; Leach and Rambaut, 1977; Leach and Rummel, 1974; Leach et al., 1974), immunologic defense and musculoskeletal and cardiovascular fitness, as well as sleep (Santy et al., 1988). All these phenomena depend on processes that reveal a broader-than-circadian spectrum of rhythms in various interactions within and among groups (Halberg, 1983; Halberg et al., in press).

Chronome alterations such as changes in circadian amplitude and/or time relations of blood pressure, heart rate and urinary markers (Halberg, 1983) signal the risks of developing sleep or emotional disturbance, neuroendocrine problems associated with different burdens, performance decrement and musculoskeletal deficiencies (e.g., bone demineralization), found in space travel. Some of these conditions related to life in a closed environment, required for travel in extraterrestrial space, also prevail for individuals isolated from society, e.g., in a cave on earth, and are pertinent to health care in physician-understaffed or deprived remote or crowded locations on earth. The recognition of the risk of silent (e.g., hypertensive and/or other cardiovascular) disease, including sudden, presumably cardiac death (Cornélissen et al., 1990), serves to institute early preventive intervention. Failure to recognize such risk on earth threatens primarily the individual. An entire mission in space may be saved by measures that prevent, e.g., depression or sudden death, apart from the absence or presence of a physician in the crew. Broadly health- and risk-related information can be obtained from a chronobiologic clinical-chemical and physiologic work station on the moon in conjunction with a comparable experimental (and an additional coordinating) center on earth.

5. RHYTHMS AND THE BROADER CHRONOME

Computer methods allow us to formulate rhythms algorithmically as recurrent patterns validated by inferential statistical means. A broad spectral structure of multifrequency rhythms includes the circadian domain of 20 to 28 hours and components with a frequency lower than 1 cycle in 28 hours, infradians, and others with a frequency higher than 1 cycle in 20 hours, ultradians. Ultradians include the about-12-hour or circasemidian component, among other harmonics of the 24-hour period that describe the circadian waveform, irrespective of whether or not these components are also responses to (or natural periods evolved in the face of) the average (e.g., 12.42-hour) period of the tides. Infradians include circadidians (with 1 cycle in ~2 days), circasemiseptans (1 cycle in ~3.5 days), circaseptans, with a frequency of 1 cycle in about 7 days; circatrigintans, with 1 cycle in near 30 days (a frequency close to that of the apparent revolution of the moon around the earth); and circannuals, with 1 cycle in about 1 year. These adjectives, referring only to cycle length rather than to any possibly underlying mechanisms, are noncommittal so as to forestall any *a priori* inference as to contributing factors. Thus, 'circatrigintan' (instead of 'lunar) and 'circasemidian' (instead of 'tidal') do not refer to any influence of the moon. This is desirable since an about-12-hour spectral component may only describe a nonsinusoidal circadian waveform. Also, in itself, any finding of the similarity or even the identity of an organismic and an environmental period can never substitute for experimental evidence of causal relations. The study of circatrigintans on the moon, with geomagnetism and the moon's gravitational effect largely eliminated, accordingly constitutes a crucial basic experiment.

6. SPECULATION OR INTUITION

An influence of the moon's revolution on human, animal and plant periodicity has been claimed for thousands of years. The Yellow Emperor's Canon of Medicine, the classic Chinese text written c. 500-700 BC, points out that the function and structure of viscera and other tissues change cyclically following a lunar periodicity; acupuncture was then administered with schedules adjusted to lunar phases. Aristotle reported a lunar influence on the activity of land and marine animals, especially on reproductive activity, and on the human menstrual cycle. The terms 'lunatic' and 'lunacy', referring to insanity accompanied by lucid intervals, are part of the English language. The earth's rotation and the moon's revolution, which have the same direction, bring each point on the earth opposite the moon once every 24 hours and 50 minutes. This periodicity of about 24.8 hours in earth-moon interaction is of particular interest because of its proximity to the prominent built-in about 24-hour cyclic (circadian) behavior characterizing most if not all physiologic variables, and since it can result in beat phenomena, providing for mood alterations as different as mania and depression (Halberg, 1960, 1968; Halberg and Cornélissen, 1991).

7. CHRONOBIOLOGY

This discipline is the study (logos) of life's (bios) time (chronos) structure revealed by rhythms and trends (Halberg, 1959, 1969, 1980, 1983; Haus, 1964; Scheving, 1976; Simpson, 1976; Cornélissen et al., 1980; Haus et al., 1983; Pauly, 1983; Reinberg and Smolensky, 1983; Hildebrandt and Geyer, 1984; Cornélissen, 1987; Pauly and Scheving, 1987); its methodology, chronobiometry, includes inferential statistical model-dependent and model-independent approaches (Halberg et al., 1988), preferably applied to data from miniaturized physiologic monitors of the freely moving human or other organisms, gauging psychophysiological status. Chronobiometry serves occupants of closed environments in recognizing risk elevation, for lowering any disease risk and thus for improving health and optimizing performance. Much can be learned from studies of small groups on earth in isolation of extended duration (Siffre, 1963; Halberg, 1968) that are pertinent to space travel and long stays in a lunar (and possibly Martian) habitat.

8. EVOLUTIONARY 'CIRCA' RHYTHMS WITH PHYSICAL (SUN-MOON-EARTH) AND SOCIETAL INPUT

The introduction of 'circa' rhythmicity (Halberg, 1959, 1969; Halberg et al., 1965) has biologic, societal, astronomical and inferential statistical implications:

• First, the 'natural' periods of the organism usually differ from those of the environment, i.e., from certain socioecologic cycles with which they have been previously synchronized. Among others, circadian rhythms, notably in core temperature, time (2-minute) estimation, urine volume, electrolyte excretion, systolic time intervals (Timbal et al., 1986), heart rate and blood pressure (Halberg, 1968; Halberg et al., 1988, 1989, 1990b; Sánchez et al., 1989), persist in human isolation, in the absence of social synchronizers. The periods differ, if slightly, yet with statistical significance from precisely 24 hours, a difference that is quite important theoretically and practically. Theoretically, a free-run, even only by a few minutes/day, or by a few hours/week or by a few days/year, is not necessarily trivial. If it is consistent and validated both time-microscopically and time-macroscopically, if, e.g., in the case of circadians, more than a full cycle is scanned by the phase and/or the phase drift can be validated by inferential statistical means, there are physiologic implications. Such results may constitute indirect evidence for a genetic basis of the rhythm (Konopka and Benzer, 1971). Practically, the cumulation of a phase drift eventually leads to greatly altered internal and external timing, which, as the case may be, is beneficial (Halberg et al., 1986), neutral or harmful.

• Second, a potential environmental influencer, if not synchronizer, may be helio-seleno-geophysical. If so, it may act in humans with a natural physical frequency near (but not necessarily the same as) that of the societal synchronizer.

• Third, for all 'circa' rhythmicity, the statistical uncertainty of estimates of period length and other rhythm characteristics is a critical inferential issue, as is any difference between the period of a rhythm and environmental cycles. As noted above, any difference between the organismic and the environmental cycle length is often slight and hence its statistical significance has to be demonstrated, of course. Ideally, the case of circaseptans, circasemiseptans and circadians, and also in the case of circasemidian periods, the inferential statistical study may have to distinguish not only a presumably average natural biologic period from one of 168, 84 and both 24 and 24.8 hours (Halberg et al., 1971) or precisely 12.42 hours (Barnwell et al., 1983b), but also periods differing from concomitantly monitored physical cycles of the sun-moon-earth system for which a biologic influence may be demonstrated or suspected, Figure 2.

• Fourth, under the same conditions, the rhythms' average periods will differ from individual to individual.

• Fifth, in the same individual, notably in isolation from society (Halberg et al., 1989), the period of each rhythm may change systematically, e.g., lengthen with time, as will the amplitude and phase of the different chronome components.

• Sixth, 'circa' rhythms with different frequencies in a given variable's chronome may be uncoupled. Thus, a circaseptan in blood pressure or heart rate that lengthens in isolation for over 4 months, as does the circadian, continues to free-run with a period differing slightly from 7 days when the circadian is resynchronized by the societal routine. Circaseptan free-running, noted first during isolation associated with amenorrhea, continued under ordinary societal conditions for blood pressure and heart rate, until these variables were 7-day resynchronized following a drug-induced return of menstruation. Both circadian and circatrigintan effects may modulate the circaseptan, a rhythm with important consequences for human health, Fig. 1 (Breus et al., 1989, in press; Halberg et al., 1989). Uncoupling of the circaseptan from the circadian component has also been documented in conjunction with the adjustment following transmeridian flights in the same variable (Hillman et al., 1988; Saito et al., 1991) and among variables (Halberg et al., 1988).

• Seventh, certain chronome components can frequency-multiply or demultiply. The phase of the weekly component of blood pressure and psychophysiologic performance series can be reset by the onset of menstruation (analyses of data by N. Murphy, 1987), so that a population mean cosinor computed with zero time given as the onset of menstruation demonstrates the circaseptan, whereas reference to fixed day of the week may not do so.

• Eighth, variance transpositions may be associated with long spans of human isolation. For performance, a prominent component at the low-frequency end of the spectrum, near 1 cycle in about 100 days, was noted during 4-month stays underground of two women, each isolated in a cave. The study of humans on the moon under conditions when geomagnetic inputs are greatly reduced, if not eliminated (by placement upon the moon and long-term stay thereupon), will be rewarding by the feasibility of examining the relations among the chronome components freed largely from geomagnetic inputs, if and only if the societal aspects of the study are also taken into account. From this viewpoint, parallel studies on rats are particularly desirable, not only because rats but not humans can serve as singly housed controls, but also since, as noted, the presumably free-running period in LL of low intensity is so close to 24.8 hours in rats.

9. IS THE BIOLOGIC WEEK ALL CULTURE?

In the case of about-12-hour, about-24-hour, about-30-day and about-yearly rhythms, the evolving organism very roughly 'matches' the length of similar geophysical periods. Do the organisms' 3.5- and 7-day periods also match environmental frequencies, namely solar-wind-generated changes in geomagnetism (Breus et al., 1989)? This possibility deserves scrutiny because of the importance of such periods in mortality and morbidity statistics, e.g., those summarized in Fig. 1 (cf. also Halberg, 1984), which undoubtedly have genetic aspects when the periods are seen in myocardial cell culture (Han et al., 1991) and in isolated platelets (Radha and Halberg, 1987). With respect to the suggestion by Breus et al. (1989 and in press) that organisms are also currently influenced by solar wind-generated changes in geomagnetic activity, it will be readily feasible to examine unobtrusively monitored blood pressure and heart rate as marker rhythms under different conditions. Of special interest are studies of a crew (I) on the moon and/or in space flight, by comparison with data of this crew on earth before and after flight, and with concomitant corresponding records of another crew (II) on earth while crew I is in space. Blood pressure and heart rate are very important markers, if indeed they help identify the elevated risk of human morbidity, not only from cardiovascular conditions as varied as stroke, myocardial infarction, sudden death, hypertensive episodes and cardiac arrhythmia, but also of asthma, epilepsy, automobile accidents and street traumata (Breus et al., 1989, in press). Not only cross-spectral coherence between the K-index and myocardial infarction, Fig. 2, deserves study, as a putative solar wind-generated effect via the earth's magnetosphere, but also changes in the interplanetary magnetic field, notably of its vertical (Bz) vector. This vector may change with a lead time prior to those changes it induces in geomagnetism that may contribute to human catastrophic and other pathology. If the Bz changes are monitored (from satellites if need be), a proper warning may eventually be issued for those at risk on earth. This warning will be the more effective the longer the lead-in-phase of the harbinger. If changes of the blood pressure and heart rate chronomes are coherent with those in the Bz component and/or with any geomagnetic indices on earth, such coherence may be altered or eliminated during space flight, whenever the crew is away from the magnetotail of the earth. Studies in space could be a definitive way to identify a geomagnetic effect which may constitute a major influencer of human pathology on earth.

10. LUNAR EFFECTS?

'Lunar cycles' have been reported in many forms of life, including human beings (Hauenschild, 1960; Neumann, 1981; Rusak, 1981; Vrána et al., 1988), beyond the use of the moon as an orientation cue (Papi, 1960; Wallraff, 1981). The gestation time of terrestrial placentals has been viewed as constituting a 30-day (circatrigintan) multiple (Brown, 1988). Lunar relationships have been considered for the magnetic response of organisms (Brown et al., 1960) and for human birth (Menaker and Menaker, 1959). We fitted a 708-hour (29.5-day) cosine curve to 2 data sets published by Menaker and Menaker (1959) concerning, in each case, the percentage deviation from the mean rate of 250,000 human births classified in relation to the lunar month. The no-circatrigintan-rhythm assumption was rejected for a set of birth in private hospitals ($P=0.002$) but not for the set from municipal hospitals ($P=0.193$). The combined data yield a statistically significant circatrigintan rhythm ($P=0.001$). Parameter tests did not reveal any inter-set difference ($P>0.10$).

The incidence of sudden infant death syndrome (SIDS) in Norway between 1967 and 1984 (Kaada and Sivertsen, 1990; 1431 cases, Fig. 3) peaks broadly, spanning, with few exceptions, the third quarter between full and new moons. A χ^2 analysis of the data contrasting the incidence around full with that around new moon does not detect a difference. If a lunar effect could be anticipated, however, a single cosinor test is applicable. Accordingly, the cosinor fit of a 29.5-day component (the idealized 'month' over which the data analyzed herein were provided in a stacked fashion) rejects the 'no circatrigintan amplitude' assumption below the 5% level (Wu et al., in press). An association with the phases of the moon of ventricular fibrillation thresholds of the canine heart in situ has been reported by Mikulecky (1986), who emphasizes that this effect was obtained for an index of pathology rather than physiology.

Abundant background data on rats are available from a decade of preparations for a rat biosatellite (Halberg et al., 1971). This evidence implicates the suprachiasmatic nuclei (SCN) and the hypothalamus and brain dehydroepiandrosterone (DHEA) and DHEA-sulfate (Robel et al., 1987) as coordinators of the chronome by feedsidewards (Halberg, 1983). The role of the SCN becomes readily apparent under two sets of conditions, namely in continuous LL and in L and darkness (D) alternating at 12-hour intervals (LD12:12). In LD12:12, the SCN are not indispensable pacemakers of the entire circadian system; with sufficient sampling and analyses, circadian rhythmicity is found to persist after bilateral lesions destroying more than 90% of these nuclei. In animals with SCN lesions kept in LD12:12, the circadian amplitudes of core temperature (Halberg et al., 1977, 1979a and b), serum corticosterone, DNA synthesis and mitosis (throughout the gut) (Scheving et al., 1983) are reduced and the acrophases advanced. In LL of low intensity, intact Minnesota Sprague-Dawley (MSD) rats exhibit a cycle in telemetered core temperature corresponding roughly to that of the apparent revolution of the moon, i.e., to 24.8 hours. This period depends on light intensity (Halberg et al., 1971) yet certainly there is a 'preference', for a 24.8-hour period under conditions of low light intensity, perhaps in some relation to an effect of the moon, as a 'preferred resonance'. The 24.8-hour period of core temperature in DD is lost in rats with SCN lesions.

It is tempting to suggest that the SCN mediates any pulling effect of the moon seen with the institution of LL, i.e., after elimination of the stronger and hence dominant synchronization by LD12:12. Data on the broader chronome of rats with and without the SCN, placed on the moon, are highly desirable with now-possible multifunctional monitoring that can be carried out for prolonged spans of isolation in space, whereas human data will be restricted to the logistically required circumstances.

It is reasoning only by analogy to compare the findings after SCN lesions to animals kept in LD12:12 of a circadian phase advance and amplitude reduction in many variables, including circulating corticosterone, with similar changes reported for 17-ketosteroid excretion in patients with emotional depression (one kind of 'lunatic') (Halberg, 1968). Observations of drastic changes in time relations among circadian rhythms in blood pressure, heart rate and core temperature are found in a woman studied in long-term isolation. These changes are assessed in longitudinal studies on the same person monitored mostly at 15-minute intervals for several months and are seen to precede the occurrence of overt depression (Halberg and Cornélissen, 1991 and unpublished). The chronobiology of depression constitutes an active field (Kripke, 1984; Wehr and Goodwin, 1981) in which longitudinal studies are indispensable.

On earth, the circadian period undergoes transient changes during the first few weeks of isolation (Halberg, 1968). Beyond the rats in LL (Halberg et al., 1970), another case of a coincidence of organismic and environmental periods is again in keeping with a possible lunar influence on body functions but does not prove this point. Wever (1988) finds for the presumably free-running (intrinsic) temperature rhythm an average period of 24.86 ± 0.21 hours and notes that it is identical to the average period of 24.84 hours of the apparent revolution of the moon. He adds that the phases of separated temperature rhythms, relative to the phase of the moon's apparent revolution, are random ($r=0.182$; $P>0.1$), concluding that the coincidence in periods is accidental. On the average, several body functions of humans kept in social isolation for spans of several months show periods close to the lunar day of 24.8 hours (Halberg, 1968).

In other individuals studied for spans exceeding 100 days, the circadian periods of core temperature, blood pressure and heart rate deviate with statistical significance from precisely 24.0 and 24.8 hours and the circaseptan rhythms of human blood pressure and heart rate deviate from precisely 7 days (Halberg et al., 1989, 1990b; Sánchez et al., 1989). This observation and the lack of phase synchronization between the reported 24.8-hour rhythms and the moon argue against a strict lunar synchronization; they do not rule out a subtle lunar influence on multifrequency rhythm characteristics. This putative influence could be exerted upon a partly endogenous period in the absence of a phase lock (Cornélissen et al., 1986a; Halberg, 1980; Schweiger et al., 1986). In further support of some lunar 'influence' is a 6-month series on core temperature in isolation; the circadian period was of 24.8 hours (Colin et al., 1967). This period is the same as the 24.8-hour average periods in the bunker studies of Wever (1988) and in the MSD rats in LL of 5 lux intensity.

A coordination in frequency but not in phase characterizes circaseptan rhythms in human transplant rejection and in unicells. The rejection episodes are more frequent on days 7, 14, 21 and 28 post-operative, irrespective of the day of surgery (e.g., whether the surgery was performed on Monday or Friday). A critical question in all of these contexts is whether there can be a synchronization or at least resonance at an (e.g., environmental) period such as 7 days or 24.8 hours (or by the same token at any other period) without a synchronization in phase of the two interactive 'influencer' and the influenced rhythm. Whether or not it is via an average frequency, but not average phase resonance, that sun-moon-earth cycles intermodulate with a societally synchronized chronome can be decided

SIDS INCIDENCE IN NORWAY (1967-1984) IN RELATION TO PHASES OF THE MOON

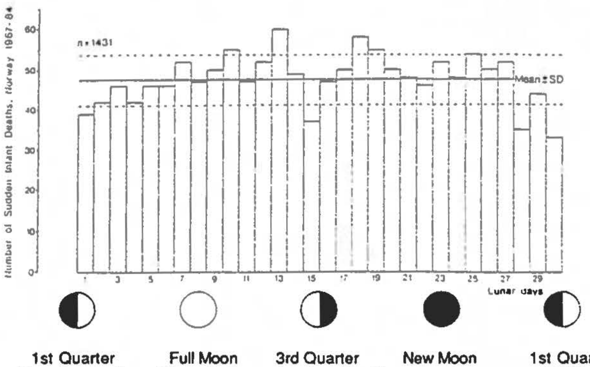


Figure 3. Number of sudden infant deaths in Norway between 1967 and 1984 exhibiting a circatrigintan rhythm when analyzed by single cosinor. (Graph prepared by Birger Kaada.) First quarter plotted twice.

if, in the near-absence of geomagnetism, the 24.8-hour period of core temperature of MSD rats is altered on the moon.

Experimental interactions of biological systems with magnetic fields are reviewed by Papatheofanis (1984, 1987). The effects of feedsidewards involving the pineal are particularly pertinent (Sánchez et al., 1988; cf. also Reuss et al., 1983, 1985; Welker et al., 1983; Olcese et al., 1985; Reuss and Olcese, 1986). In addition, Easterly (1982), based on the physical principle of pressure loss when a conductive fluid moves through a magnetic field, has implied a direct corrective effect by estimating an increase, in the presence of a magnetic field, of blood pressure in the major arteries. Along with epidemiologic data, he estimates the risk for blood pressure-related health effects resulting from exposure to magnetic fields. Gorczynska and Wegrzynowicz (1983) add another dimension to putative magnetic field effects by experimental evidence for increased platelet aggregation, increased prothrombin and partial thromboplastin times, decreased fibrinogen and increased fibrinolysis by exposure to certain magnetic fields, suggesting that these exposures result in a tendency toward hemorrhage and thrombosis. Thus, multiple (clotting and mechanical; Easterly, 1982) effects upon the circulation and indirect effects via the pineal, among others, may contribute to a correlation between heart attacks and magnetic activity, repeatedly affirmed (Malin and Srivastava, 1979) as well as disputed, e.g., by Knox et al. (1979), who found serial correlations of daily admissions for acute myocardial infarction at 7, 14 and 21 days, 'mainly characterised by a deficiency of admissions on Sundays.' Clearly, the opportunity must be seized to study organisms freed largely from geomagnetism, e.g., on the moon.

11. SPECULATIVE EFFECT OF A RING AROUND THE EARTH

Elementary astronomy texts indicate a gradual long-term increase in day length by virtue of a slowdown of the earth's rotation around its axis. A lengthening of the organism's circadian period may have occurred more rapidly than the lengthening of the geophysical day. Circadian periods that are longer than the terrestrial period, now 24 hours, are encountered in a number of organisms under several conditions. Can it be that an overshoot lengthening of the biologic circadian period occurred because organisms are so structured in time that, according to different lines of evidence, it is easier for several contemporary life forms to delay a rhythm than to advance it? The opposite, namely a faster advance than delay, at least in the rate of adjustment, is found as well (Aschoff and Wever, 1966; Koukkari and Halberg, 1973).

Conceivably, an evolutionary advantage of a free-running period near 24.8 hours or a resonance (with a lunar effect, without phase-synchronization at precisely 24 hours) might lie in this period's tendency to prevent the individual from locking into some period shorter than 24 hours. Animals that could respond to influencers, if not synchronizers, at 24.8 hours had positive adjustment value. At one time the earth may have had a ring around it which had not yet pulled into the plane of the equator (O'Keefe, 1985, 1986; O'Keefe and Sullivan, 1978). Then, under the influence of the attraction of the earth's equatorial bulge, the plane of the ring slowly regressed; that is, it precessed in the negative direction. The result may have been that the period from one meridian passage of a point on earth to the next was slightly less than 24 hours. Thus, the effect of the near-24.8-hour free-running period may have discouraged locking-in on a period such as 23.9 hours. The ring system, when formed, was probably much brighter than the full moon, which has been reported to be capable of disturbing sleep. During the day, the sun would have been eclipsed by the ring; the time of eclipse would have been governed by a period shorter than 24 hours (by something like 1% in some cases). If one became locked into the ring day, it might mean to some (personal communication) that one would become drowsy at some inappropriate moment. Thus, there would be an advantage if one locked on to longer rather than shorter periods (personal communication; cf. O'Keefe, 1985, 1986). Mice, with periods shorter than 24 hours, did not derive any such advantage, but seem to be fit nonetheless. The ring hypothesis certainly is less attractive than is some lunar influence 'pulling' natural periods at a low light intensity in LL toward 24.8 hours in some species such as rats (Halberg et al., 1971), but not in others such as mice (Halberg, 1959).

12. 'TIDAL' OBSERVATIONS

Interactions between circadians and circasemidians (specifically, about 12.4-hour rhythms related to the tides) have been studied on the fiddler crab, among other marine animals (Barnwell, 1976; Barnwell et al., 1983a, 1983b, 1988; Brown, 1960; Fingerman, 1960). For instance, a 41-day series of locomotor data, obtained from a female specimen of *U. minax*, held in a small tilting pan actograph exposed to the natural cycle of illumination, had been saved by one of us (FB) for reanalysis. Linear-nonlinear least-squares rhythmometry yields on these data, Fig. 4, 1 circasemidian and 2 circadian statistically significant (but not necessarily scientifically signifying) components with their 95% confidence limits, Table 1.

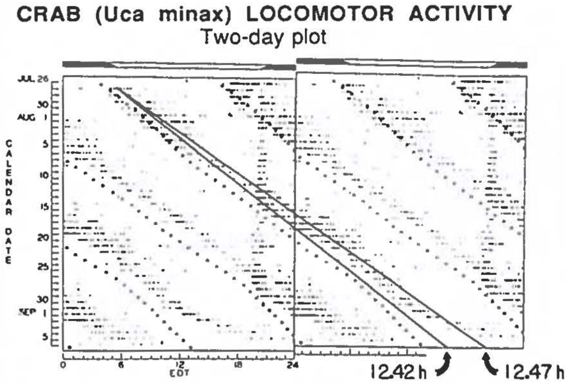


Figure 4. Two-day (double) plot showing approximately four tidal cycles of activity of a female crab held in a small tilting pan actograph exposed to the natural cycle of illumination. The small circles represent the tides predicted from U.S. Government tabulations preceding times of high tide for the habitat (Tide Tables, 1966), the 12.42-hour line corresponds to the slope corresponding to the average tidal period predicted and the 12.47-hour line to the best-fitting circasemidian period.

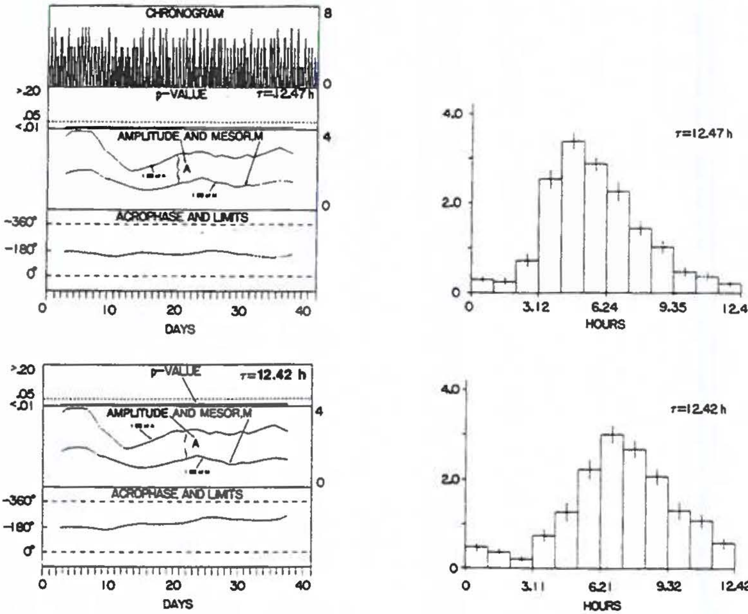
TABLE 1. ESTIMATES OF RHYTHM CHARACTERISTICS AND THEIR 95% CONFIDENCE LIMITS FOR THE LOCOMOTOR ACTIVITY OF A FEMALE CRAB *(UCA MINAX)*

Component N	Period (hour)	Amplitude ('activity'/hour)
1	12.47 (12.46, 12.48)	1.46 (1.10, 1.83)
2	24.05 (23.95, 24.15)	0.59 (0.22, 0.95)
3	25.94 (25.79, 26.09)	0.44 (0.07, 0.81)

The persistent 12.47-hour period in locomotor activity differs ($P<.05$) from the 12.42-hour period of the principal lunar circasemidian ('semidiurnal') M_2 harmonic constituent of the tide in the crab's original habitat. This is evident from:

- the lack of overlap of the 95% confidence region for the 12.47-hour period with the 12.42-hour period of the M_2 constituent;
- a chronobiologic serial section analysis (Halberg, 1969) of the data on locomotor activity. The top of Fig. 5 shows that the acrophases resulting from the fit of a 12.47-hour period follow a more or less horizontal course, whereas the acrophases from a 12.42-hour fit occur later and later as time advances. This finding indicates that the period is longer than precisely 12.42 hours. The latter is the predicted constituent of the tide in the crabs' original habitat, exhibited by small circles in Fig. 4. It should be realized further that the 41-day series is of sufficient length to document that the 12.47-hour period differs from the 12.42-hour average period represented by the circles. More specifically, the shorter variations of the circles notwithstanding, and even though the 12.47-hour period may be within the range of such short-term variations, as an *average*

CRAB (Uca minax) LOCOMOTOR ACTIVITY
CHRONOBIOLOGIC SERIAL SECTIONS (LEFT) & PLEXOGRAMS (RIGHT)
Summary at two trial periods (τ)



*Vertical scale for chronogram, plexograms, MESORS and amplitudes in arbitrary activity units.

Figure 5. Two different methods, chronobiologic serial sections (left) and plexograms (right), with 2 different trial periods, demonstrate that the presumably natural average period of the crab's activity (12.47 hours) (shown in Fig. 4) differs from the period of the tide (12.42 hours), though it may transiently phase-lock from time to time.

period it differs with statistical significance from a precisely 12.42-hour period (as documented by a confidence interval in Table 1);

• time-macroscopically, in the upper left of Fig. 4, the 12.47-hour line follows the slope of the major bursts of activity dots better than the 12.42-hour line.

• Again macroscopically, on the right of Fig. 5, the plexogram corresponding to 12.47 hours has a higher peak than that corresponding to 12.42 hours.

Other periodic components of interest in relation to the complex orbital motions of earth, moon and sun are the tidal periodicities in the range of 27 to 30 days (Neshyba, 1987), including the 29.53-day synodic, the 27.32-day tropical and the 27.55-day anomalistic monthly constituents (Barnwell, 1968, 1979). Moon quakes also exhibit circatrigintan components (O'Keefe, 1985, 1986; O'Keefe and Sullivan, 1978). Such periodicities may contribute to the expression of circaseptan components which may be reinforced by their harmonic relation to circatrigintans. The concomitant monitoring of physiological variables on earth and on the moon (on experimental animals under free-running conditions) may shed light on any contributions of earth/moon interactions to the 24.8-hour periodicity. Such studies may thus be informative concerning the folkloric reference to some mentally ill individuals as 'lunatics'; even if a primary effect does not stem from the moon ('luna') as such, there may be in certain patients a shift in physiologic dynamics (gauged by the variance) from the predominance of factors related to a solar day (Halberg et al., 1955; Halberg and Cornélissen, 1991) and/or a social (socioecologic) ordinary day to the preponderance of a lunar-day influence.

13. NATURE AND (NOT VERSUS) NURTURE

Genetic components of human heart rate rhythms are documented on twins reared apart (Halberg, 1983; Hanson et al., 1984). Nonetheless, organisms are systems open to changes in prominence of any geomagnetic, gravitational or other environmental 24.8-, 84- or 168-hour or other periodicity that may influence the relative amplitude and/or frequency of spectral components with nearly corresponding periods. Even though any such sun-moon-earth effects may not synchronize biological rhythms in health, they may influence them in terms of period 'pulling' if not phase locking. The effects to be examined on the moon are primarily subtractive rather than additive; the gravitational forces and/or electromagnetic fields on the moon and on Mars are only a fraction of those possibly affecting physiologic rhythms on earth.

Results from long-term studies on human isolation from society reveal a major alteration in the prominence of various spectral components. While some low-frequency infradians are more prominent, components with a period of about 7 days, those with a period of about 12 hours and circadians are reduced with respect to their prominence on a social (24-hour and weekly) routine (Halberg et al., 1989, 1990b). During social isolation, the variance attributable to a given component is substantially smaller than in the presence of a social routine. The amplitude (a measure of the extent of predictable change within one cycle) during isolation is only a fraction of that during ordinary life. Studies on the moon may clarify to what extent the built-in, environmentally-synchronized (or free-running) periodic components of human (and murine) physiologic rhythms, and large variance transpositions in and among several spectral domains, are similar for the cardiovascular, neuromuscular, neuroendocrine and metabolic systems on earth and on the moon.

14. OPPORTUNITIES

By studying the same individuals on earth and on the moon and/or on Mars, a dose response to gravity (g) can be tested, with microgravity en route and 1/6 g and 1/3 g on the moon and on Mars, respectively. Concomitant controls on earth would allow an assessment of age effects on a much larger sample at 1 g, a topic of a now-planned lifespan study. Even if the same individuals cannot be tested at all g forces, a response curve may still be constructed in a transverse (cross-sectional) or preferably in a hybrid (linked transverse and longitudinal; Halberg et al., 1971) fashion by using the flight crew data before liftoff and after return as longitudinal control and comparisons with a comparable crew remaining on earth as a transverse control. In this context, the data from the lunar and Mars missions can be interpreted in relation to the hybrid reference standards at 1 g on earth.

A lunar human habitat and chemical laboratory offer the opportunity to scrutinize the effects, if any, of this satellite upon the mammalian chronome. Concomitant complementary human or murine information is likely to be valuable. To study a full spectrum of biologic rhythms, including circannuals, long-term physiologic monitoring of astronauts or cosmonauts should become a sine qua non for acceptance into the program. Even should this goal be achieved, a study on rats would remain invaluable for both basic and applied aims. Work on experimental animals allows, with far-reaching standardization of both genetics and the environment, tests of resistance to possible injury such as endotoxins (Halberg, 1969) that are not applicable to human beings. The 'noise' from human genetic and epigenetic heterogeneity is reduced by the use of inbred rat strains explored for their spectrum of rhythms by life-span studies carried out in preparation for a biosatellite mission (Halberg et al., 1971) and thereafter (Halberg J. et al., 1980) and the standardization of the environment (Holley et al., 1988). Telemetry can be used to study rats sent up pregnant to study the time course and duration of the pregnancy of rats on the moon and their ability to deliver and separately the ability of nonpregnant rats to become pregnant on the moon. The growth and development of the first lunar offspring will be of interest with physiologic telemetry added once the rat reaches adult weight.

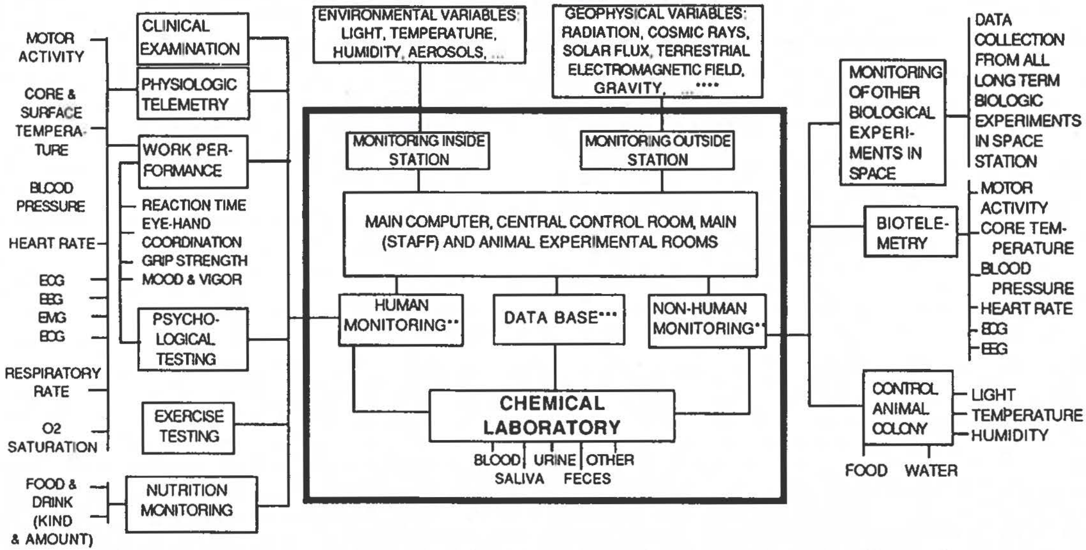
Under different gravity conditions and under conditions associated with an alteration in environmental periodicities on earth, en route and on the moon, a lunar project can examine any changes in the behavior of different spectral components of rats kept under constant environmental conditions, housed singly, in pairs, and in groups of 4, 8 and 12 individuals. Human isolation studies of short duration on groups have already revealed interesting social synchronization (Apfelbaum et al., 1969). The cardiovascular and metabolic monitoring of the human crew will provide chronobiologic indices of any psychophysiologic burden associated with the conditions on the lunar habitat (Halberg and Cornélissen, 1991).

15. PROPOSITION

A work station for chronobiologic research sketched in Scheme 1 could comprise a clinical chemical laboratory and a human physiologic and environmental monitoring system. Several orders of rhythms can then be studied: spontaneous, reactive and intermodulatory (Halberg, 1983). Reactive rhythms can be studied when an exercise system is on board. The merits of timing exercise have been documented (Halberg et al., 1988; Levine et al., 1977; Stephenson et al., 1984; Wenger et al., 1976). Human (and murine) motor activity, core temperature, blood pressure, heart rate, other ECG endpoints such as height of P, R and T, eye movements and EEG features are characterized by a spectrum of rhythms with different frequencies (Cornélissen et al., 1986b; Quadens and De Lee, 1974; Quadens and Green, 1984; Tarquini et al., 1982), as are urinary calcium, sodium, potassium (Sothern and Halberg, 1981; Sothern et al., 1974, 1987), catecholamines (Descovich et al., 1974a and b; Reinberg et al., 1970), melatonin (Wetterberg et al., 1986) and other hormones and hormonal metabolites (Halberg et al., 1965, 1981a), many of them also accessible noninvasively. The crew's psychophysiologic variables, automatically monitored when possible, can serve to ascertain crew health, to optimize performance and work, and to detect and manage earliest risk by chronobiologic approaches, including focus upon undue physical or mental loads. Ultradian and infradian as well as circadian rhythms in these variables,

SCHEME 1: LUNAR-BASED CHEMICAL ANALYSIS LABORATORY (LBCAL)

ANALYTICAL RESOURCE FOR CHRONOBIOLOGIC HEALTH AND EXPLORATION OF SPACE (ARCHES)*



*Provides information about environmental cycles and events in artificial lunar or vehicle environment and outside, relates this information to organismic rhythms from two sources and, if need be, acts accordingly by optimizing schedules or prompting other, e.g., health-related measures.

**And corresponding reference data base for interim analyses.

***Archives for storing all original data and interim results and for updating of the latter results for biochemical laboratory and corresponding data base.

****Instrumentation permitting.

once they are mapped in relation to risk (a task yet to be completed) allow the derivation of sensitive gauges of health in the form of time-targeted single samples (Halberg, 1983).

For longitudinal human and murine monitoring, circadian focus will have to be extended to circasemiseptans and circaseptans, with appropriate unobtrusive monitoring instrumentation for blood pressure and heart rate, among other variables yet to be integrated into a computerized system. The broader chronome is also to be studied with concomitant provision of geomagnetic information under appropriate conditions of L and D on inbred Fischer rats (Halberg et al., 1981b). In rats, the behavior of circadian-circaseptan rhythms in the above-listed variables could be studied concomitantly in DD in LD12:12 and in LL of various L intensities in order to determine in which condition, if any, correlations with a geomagnetic K index and with the Bz component of magnetic induction can best be detected. By monitoring the rat, the spectrum of physiologic variables such as the EEG, ECG, blood pressure, total activity and temperature, the most sensitive variables, may be determined by the criterion of their sensitivity to any geomagnetic changes. Instrumentation now available for a multi-variable monitoring of adult rats combined with past results from a very large investment of funds and time into lifelong core temperature profiles (Halberg et al., 1971) provide an invaluable background for the development of the most pertinent, truly unobtrusive instrumentation for continuous use by the astronaut.

16. DISCUSSION

If flightworthy systems can be procured, work with a multimicroelectrode-cell culture device, constructed by one of us (JH), could be used to monitor the electrical activity of neuroendocrine cells such as those of the pineal and the SCN, as gauges of cellular response to alterations of the sun-moon-earth environment (Breus et al., 1989 and in press). Myocardial cell culture is particularly attractive since circasemiseptan components have been demonstrated to characterize a single cell and aggregates of cardial myocytes in culture (Han et al., in press). The exploration of basic mechanisms of sun-moon-earth effects on the chronome could then be carried out *in vitro* as well as *in vivo* with focus on underlying (feedsideward) interactions (Halberg, 1983).

The literature covering space biology and medicine reports endocrine abnormalities in relation to the 'space' adaptation and motion sickness syndromes (Doppelt, 1989; Holland, 1989). The proposed laboratory research will derive sensitive chronobiologic endpoints for the load ('stress'-'strain')-related variables and for metabolic and immune variables, all exhibiting a broad multifrequency rhythm spectrum. To cite but one example, the cortisol amplitude-acrophase pair may show an alteration before the MESOR does in a genetically determined case of hypercortisolism (Angeli et al., 1987). Systematically collected and analyzed endocrine time series based on urine and saliva and/or timed spotchecks on blood, have revealed that rhythm characteristics can constitute endocrine classifiers of the risk of developing diseases such as myocardial infarction and stroke (Halberg et al., 1981a; Halberg, 1983; Hermida et al., 1990). Clinical laboratory variables, by virtue of their rhythm characteristics, can be harbingers of trouble, in conjunction with other chronobiologic endpoints, such as those of the ECG. For example, the circadian amplitude-acrophase pair of electrocardiographically recorded ventricular ectopic beats serves (when conventional endpoints fail) as a (group-based) harbinger that precedes sudden death by years (Cornélissen et al., 1990; Orth-Gomér et al., 1986). The likelihood for sudden death may be small, but if it occurred in a crew of four or eight and if it involved a member critical for a long-term mission, it will mean the difference between mission success and failure. The chronobiologic ECG interpretation is but one of a long list of bellwethers that may be available with minimal turn-around time from the lunar clinical chemical laboratory (Halberg et al., 1981a, 1989).

Selected chronome characteristics critically determine responses to stimuli (Halberg, 1962, 1964; Halberg et al., 1955). They represent harbingers of elevated risk (Halberg et al., 1981a). More broadly, however, for any biochemistry, the dynamics expressed as rhythms provide novel information. When one focuses upon urine, the biologic variation is between 50% and 100% around the mean. This means that a reduction of the technical error, e.g., from 10% to 1% or less, will amount to little progress, unless the 50% to 100% change accounted for by the rhythmic structure of urinary variables is properly accounted for and exploited. Exploitation of any analytical progress thus will be dependent upon concurrent progress in dealing with the chronome. Once they are resolved, rhythms and trends represent new endpoints providing information within the physiologic range on disease risk (Halberg et al., 1981a) and constitute sensitive gauges of loads imposed upon the organism (Halberg, 1964), whether physical (Halberg et al., 1955) or other (Halberg, 1962; Halberg et al., 1988).

17. SUMMARY AND CONCLUSION

A lunar clinical-chemical laboratory in conjunction with physiologic monitors on the crew (in lieu of conventional sphygmomanometers and thermometers) and a chronobiologic data analysis capability would serve as a critical component of a telehygiene system designed to detect chronome alterations as classifiers of risk, prompting preventive action, with unobtrusive blood pressure and heart rate monitoring of the crew's chronomes as principal marker rhythms at the outset. Results could be compared with those of well-matched controls living under simulated lunar conditions on earth. A parallel study on rats could further quantify any chronome alterations on the moon, under different experimental conditions. Components of particular interest are the circadian, circasemiseptan and circaseptan rhythms under synchronized and (in experimental animals) under free-running conditions. The logistically important mission, as a stepping stone to Mars, would then provide invaluable information in itself on any effect of a drastic reduction if not elimination of the gravitational or magnetic cyclic forces acting on earth. Future space crew members (at entry into the program) could be asked to be test pilots not only in space but also in chronobiologic exploration by automatic long-term physiologic monitoring on earth. Invaluable control data could be had for greater safety of the missions to the moon and thence to Mars and for the basic science question of any lunar effects related to health, with a spin-off critical also for our understanding of physiology on earth and for lowering the risk of cardiovascular and other diseases.

DEDICATION

This chapter honors a colleague in endocrine chronobiology and friend: the late Frank Brown Jr. His once-unorthodox views are here integrated into testable feedsidewards from geomagnetism, influencing the genetically anchored and socioecologically-synchronized chronome. Any geomagnetism-mediated solar wind influence upon the societally synchronized chronorisk of a human myocardial infarction, stroke and other morbidity and mortality constitutes a challenge to research in space and on earth.

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EPILOGUE

Monitoring blood pressure in space flight in general and notably on the moon deserves a major effort for telehygiene, irrespective of whether this variable also picks up any effects of the sun-moon-earth system. For a possible effect of solar wind, a record of Bz-GSE has been analyzed. It was provided by Joseph H. King, Head, National Space Science Data Center (NSSDC) (Goddard Space Flight Center, Greenbelt, Maryland 20711, USA) (from the OMNI interplanetary data base). These data are collected by the IMP-8 satellite. The Bz series were subjected to linear-nonlinear least-squares rhythmometry and cosinor analysis (Halberg, 1969). There was no detectable precise 168-hour, precise 84- or precise 24-hour feature in the time series of Bz during a 16-month span corresponding to a span when blood pressure and heart rate data were available (July 14, 1987-November 20, 1988) on a 67-year-old woman, EH. This was the case whether spectra were computed over the whole span or averaged over 8 consecutive 2-month sections by population-mean cosinor and whether the series was approached as a line or a continuous spectrum. A circatrigintan component with an amplitude of .3 ± .1 nT was found, with a period of 631.2 hours (26.30 ± 0.16 days) and a conservative 95% confidence interval (CI) extending from 623.8 to 636.6 hours (25.82 to 26.78 days). By population-mean cosinor, a <u>circa</u>semiseptan component more prominent than the circatrigintan was found to have an amplitude of .46 ± .07 nT. It had a period of 83.5 hours (3.48 ± .01 days) and had a 95% confidence interval that did not overlap precisely 3.5 days, extending from 3.47 to 3.49 days. A component with a period of 164.7 hours also stood out (P=0.038). Statistical significance spanned the region of trial periods at .1-hour intervals from 164.4 to 165.5 hours. A component with a similar period of 164.4 hours was found earlier for the K index during 1979-1981, also by population-mean cosinor.

A circasemiseptan component was detected only as a secondary peak for the systolic but not for the diastolic blood pressure or heart rate of EH. For heart rate and systolic and diastolic blood pressure of EH, the zero circaseptan amplitude assumption was rejected with statistical significance. The circaseptan (vs. circasemiseptan) amplitude for the physiologic variables was larger. For the physiologic variable, the statistical significance regions cover the precise week, except for the case of heart rate. For systolic blood pressure, this region extends from 167.8 to 170.0, and for diastolic blood pressure from 167.9 to 169.9 hours. Even in the case of heart rate, the statistical significance region from 166.8 to 167.9 hours differs only by 0.1 hour from 168 hours. The societal week may lock-in a built-in circaseptan whereas the circasemiseptan feature of the blood pressure of EH and perhaps of many other phenomena, including the incidence of myocardial infarctions, resonates near one or the other circasemiseptan, which is not of precisely 84-hour length. (There were two peaks *near* 84 hours in the Bz spectrum during the span investigated.) Genetics, society and the cosmos, the latter via geomagnetism, all shape our physiology and, in view of the evidence in Figures 1 and 2, affect our pathology.

An intermittency of circaseptans and circasemiseptans characterizes population and individual time series, for instance the time series on myocardial infarction prompting ambulance calls in Moscow (Breus et al., 1989). Spans in which neither a circasemiseptan nor a circaseptan component could be detected represent about one-third of the three years; the circaseptan and/or the circasemiseptan component were detected by the concomitant fit of 3.5- and 7-day cosine curves two-thirds of the time (Table 2). These components are prominent in the case of myocardial (continued on p. 33)

TABLE 2: IN 66.6% OF A 3-YEAR RECORD OF DAILY INCIDENCE OF MYOCARDIAL INFARCTION (MI), CIRCASEPTANS AND/OR CIRCASEMISEPTANS CHARACTERIZE MI WITH *AN ALTERNATION OF CIRCASEMISEPTAN AND CIRCASEPTAN PROMINENCE* IN PART OF THE TIME SERIES*

Calendar time	None detected	Circaseptan spans (days)	Circasemiseptan	Both
01/01-01/28/79				28
01/29-02/25/ "		28		
02/26-04/23/ "	56			(28)
04/24-05/21/ "			28	
05/22-07/16/ "		56		(28)
07/17-08/13/ "			28	
08/14-10/08/ "	56			
10/09-11/05/ "		28		(28)
11/06/79-01/28/80	84			
01/28-10/06/ "		252		
10/07/80-01/26/81	112		(28)	
01/27-02/23/ "			28	
02/24-03/23/ "		28		
03/24-04/20/ "	28			
04/21-06/15/ "			56	
06/16-09/07/ "	84			
09/08-10/05/ "			28	
10/16-11/03/ "		28		
11/04-12/28/ "	56			
Total: 1092 days				
Percentage of total days	43.6 (35.9)	38.4	15.4 (17.9)	2.6 (10.3)

*Results from chronobiologic serial section analysis. A 7-day and separately a 3.5-day cosine curve were fitted to consecutive 28-day intervals of the series displaced with 28-day increments in data consisting of the number of cases prompting telephone calls for ambulances for conditions diagnosed as MI for the span 1979-1981 in Moscow, USSR. ( ) denotes results from concomitant fit of 3.5- and 7-day cosine curves.

(continued from p. 32) infarctions or other patterns of pathology in human populations. A circatrigintan component characterizes 293 (out of 575) attacks of tachyarrhythmia that were accompanied by organic heart disease (Mikulecky, 1986, 1990) and a circadiseptan rhythm the appearance of functional tachyarrhythmia. Mikulecky suggests scrutiny of a lunar cycle and its first two harmonics in the occurrence of tachyarrhythmia attacks with differentiation between the organic and functional disorders. He invites the collection of time series for rigorous analyses of infradians in pathology (Mikulecky, 1986) and physiology (Mikulecky et al., 1986). The alternation in prominence of different infradian components, documented in Table 2, may be kept in mind.

More work remains to be done: dense, preferably beat-to-beat automatic monitoring of blood pressure over long spans in humans and rodents is now feasible. Blood pressure can be proposed as a candidate physiologic marker of solar wind effects exerted via geomagnetism on humans. On theoretical grounds, this was indicated already in 1982 by Easterly. Blood pressure monitoring on the moon, where, as described by Sonett (1988), the situation may be complex, could shed light on effects of magnetic fields on the cardiovascular system by exposing astronauts to systematic changes as the moon enters and leaves the earth's magnetotail. According to Joseph H. King (1986 and personal communication), during 18 days of a lunar cycle, while the moon is in the solar wind, its magnetic field may approximate 5 nT, whereas the field about doubles while the moon is in the earth's magnetotail. The entry and departure of the moon from the earth's magnetotail may provide the needed contrast in selected lunar sites.

More specifically, the lunar magnetic field $\bar{B}_A$ is the vectorial sum of magnetic fields of different origins, each of them varying in magnitude according to the relative position of the moon with the earth and to the intensity of the solar wind. According to Dyal and Parkin (1971), $\bar{B}_A$ can be expressed as:

$$\bar{B}_A = \bar{B}_E + \bar{B}_\mu + \bar{B}_S + \bar{B}_T + \bar{B}_P + \bar{B}_F + \bar{B}_D.$$

$\bar{B}_E$ is the total external (solar + geomagnetic) field.

$\bar{B}_\mu$ is the magnetization induced in the moon by the external field $\bar{B}_E$ as the moon is a paramagnetic body with magnetic permeability $\mu \cong 1.029$ (Dyal et al., 1973). $\bar{B}_\mu$ has a dipole-like configuration, with the dipole moment aligned with the external field.

$\bar{B}_S$ is the magnetic field produced by local distributions of magnetized material on the lunar surface. This field varies widely from site to site, having a magnitude of 4 nT at the Apollo 15 landing site (Hadley Rille) and reaching a magnitude of 300 nT at some of the Apollo 16 measuring stations (Descartes region). This field increases with the density of the solar wind due to the effect of magnetic compression. It is believed that large increases of the lunar magnetic field are caused by interactions of the solar wind with some local magnetic anomalies when they reach the lunar terminator (limb compression) (Russell et al., 1973).

$\bar{B}_T$ is the toroïdal field induced by the current generated by the movement of the moon in the magnetic field $\bar{B}_E$. It is therefore dependent upon the solar activity and upon the position of the moon in the earth's magnetosphere.

$\bar{B}_P$ is the field generated by the eddy currents in the lunar interior when the moon crosses regions of time-changing magnetic fields, i.e., when the moon crosses the current rings and the different plasma flows in the earth's magnetotail. This field opposes the change in the external field. It is compressed by the solar wind on the dayside and elongated downstream in a way similar to the earth's magnetosphere. When triggered by a sudden variation in magnetic field, this field decays with a time dependence function of the electrical conductivity of the lunar interior.

$\bar{B}_F$ is the magnetic field associated with the hydromagnetic solar wind and $\bar{B}_D$ is the diamagnetic field associated with the creation of a cylindrical plasma cavity behind the moon.

On the lunar dark side, $\bar{B}_F$ and $\bar{B}_\mu$ are very small and there is no magnetic compression effect. The geomagnetic tail lobes are the best places to observe the unperturbed lunar magnetic field as the plasma density is very low, the magnetic field is weak and steady, reducing the contribution of the different magnetic fields to $\bar{B}_A=\bar{B}_S+\bar{B}_\mu$ (Lichtenstein et al., 1978).

In terms of mechanisms through which geomagnetic effects may be perceived, the pineal comes to mind as a very sensitive human receptor which apparently responds to variations of the order of a few nT, induced by solar winds via the magnetosphere. Frequencies of the order of about 60 Hz (e.g., the power line frequency) have been reported to disturb the circadian production of melatonin, and pulsed static magnetic field exposure at night has been reported to reduce pineal melatonin production by suppressing N-acetyltransferase activity (Reiter, 1991a-c; cf. also Lerchl et al., 1990, 1991a,b; Leung et al., 1990; Olcese et al., 1985; Reuss and Olcese, 1986; Reuss et al., 1983, 1985; Semm, 1983; Welker et al., 1983; Wilson et al., 1981, 1986). A circaseptan modulation of the amplitude of the free-running circadian rhythm in RIA-assayable melatonin from the isolated pineal of lizard kept in continuous darkness was found by analyses of published if too-limited data by Halberg (1983). A time-macroscopic infradian modulation is shown for melatonin production by the chicken pineal in superfusion studied by Leung et al. (1990) in LD12:12. The pineal, which exhibits both prominent circadian and circaseptan rhythmicity (Vollrath et al., 1975; Vollrath, 1982), may thus be a receptor of geomagnetic effects, acting perhaps in a fashion akin to pineal feedsidewards with the pituitary and the adrenal (Halberg, 1983; Sánchez et al., 1982, 1988). The circadian MESOR of urinary melatonin excretion by clinically healthy women correlates positively to risk of developing high blood pressure and other cardiovascular diseases (Wetterberg et al., 1986).

Direct vascular mechanisms may also be involved in the Bz effect on human blood pressure. The role of iron in the special environment existing in hemoglobin as a potential receptor may also be considered (Weissbluth, 1974). Another mechanism by which fields couple to the cell may be through the mediation by the cell membrane and/or large proteins that float in it, acting as a cooperative physical system: such a transduction mechanism may be capable of signal amplification and may require the biological equivalent of coherent detection (Nair and Morgan, 1990).

Psychosocial lunar effects must also be considered. An about-yearly (circannual) (Doe et al., 1986; Halberg, 1969; Halberg et al., 1981) change characterizes (with the about-24-hour or circadian [Halberg, 1969; Halberg et al., 1959, 1981a] and episodic or ultradian variation) glucocorticoid concentration in human serum and is recorded in around-the-clock profiles from 130 children, 8-15 years of age, sampled during 5 years in different seasons in La Coruña, Galicia, Spain. Blood for circulating cortisol radioimmunoassay was drawn from a given child at 3-hour intervals during a single 24-hour span. To a set of 8 values/child, a 24-hour cosine curve was fitted (Halberg, 1969). Thus, one obtained, for each series, a midline-estimating statistic of rhythm or MESOR, and measures of the extent and timing of predictable (insofar as circadian rhythmic) change, the circadian amplitude and circadian acrophase, respectively. Each circadian characteristic of a given series was then assigned to the calendar date of sampling, to obtain 3 time series, one consisting of circadian MESORs, another of circadian amplitudes and a third series of circadian acrophases. To each of these 3 series, a 365.25-day cosine curve was fitted. Thereby, possible about-yearly changes in any one of the characteristics representing the entire data set of over 1000 samples could be sought separately. For the series of the circadian cortisol amplitudes, the zero circannual amplitude assumption was rejected and a circannual cortisol rhythm thus demonstrated. To assess the waveform and test for the presence of any other unanticipated periodicity, a least-squares spectrum was obtained, providing estimates (continued on p. 37)

TABLE 3: ABOUT-YEARLY AND ABOUT-30-DAY MODULATIONS OF CIRCADIAN SERUM CORTISOL AMPLITUDE (NG/DL) IN 130 CHILDREN IN LA CORUÑA, GALICIA, SPAIN, STUDIED IN THE COURSE OF 5 YEARS (1985-1990)*

Period (hr)	MESOR ± SE	N subj. (total) [samples]	PR	P (2A=0)	Double amplitude (A) ± SE of 2A	Acrophase (95% CI)	P-values gofit	normal	hom
8766	6.4 ± .208	130 (8)	6	.015	1.7 ± .56	-319° (-281, -358)			
708		[>1000]	4	.038	1.4 ± .52	-220° (-176, -263)			
both			10	.011			.329	.055	.862

*Data from 3-hourly samples covering 24 hours were fitted with a 24-hour cosine curve. A measure of one-half of the extent of predictable change, namely the circadian amplitude, was thus obtained for each child. This circadian amplitude was assigned to the calendar date of sampling and was fitted concomitantly with two periods, one of 8766.00 hours (=1 year) and another of 708 hours (=synodic lunar month). Phase reference: midnight December 22 of the year preceding data collection. PR=percent rhythm. gofit=goodness of fit; normal=normality of residuals; hom=variance homogeneity. These three regression diagnostic tests are in keeping with the assumptions underlying the analysis here presented.

(continued from p. 36) not only for the 1-year component tested, but also for its 25 harmonics. For the circadian cortisol amplitude, only two candidate modulatory cycles were found, one predicted with a 1-year (P<0.014), the other (not predicted) with a 708-hour (P=.029) period corresponding to the synodic lunar month, Table 3. These ordering P-values for rhythm detection were obtained when these two components were fitted concomitantly. Regression diagnostic tests did not invalidate the result (Table 3). An endogenous component of an about-yearly change has a precedent: a circannual rhythm persists with a phase drift, if not a free-run, in the weight of the ovary of catfish kept for several years in continuous darkness, in continuous light or on a fixed photofraction (Sundararaj et al., 1982). There are other important time-macroscopic reports on circannual rhythms as well (Pengelley and Asmundson, 1974; Pengelley and Fisher, 1963; Zucker, 1988).

By contrast to the results on the data from Galicia, Spain, no synodic lunar month effect was found in circulating cortisol data (covering 24 hours at 20-minute intervals in each of 4 seasons) from clinically healthy women in Kyushu, Japan, and Minnesota, USA. Any direct effect of the moon, e.g., by light, gravity and/or electromagnetic field, should also be found in the USA and Asia. Agricultural and, in coastal areas, fishing activities are scheduled according to a lunar calendar in Galicia, but not in Kyushu or Minnesota. The social schedule may be largely responsible for the 'lunar' component in circulating cortisol of Galicians, or rather one may deal with the socio-ecologic synchronization (Halberg et al., 1959) of about-monthly changes built into the organism. The about-30-day 'lunar' modulation of serum cortisol may be a feature of a budding social chronobiology. Since plans are being made for a human return to the moon, the critical test of the origin of the 708-hour modulation is possible on the moon itself, where any physical effects of the moon exerted upon inhabitants of the earth are largely reduced, if not eliminated. Serial saliva collection for cortisol determinations may be of interest to space travelers.

The question remains as to whether the observation reported herein pertains to many aspects of cardiovascular and other human pathology, suggested as being related to cosmic factors (Stoupel, 1979; Stoupel and Shimshoni, 1986; Kuritzky et al., 1987; Merlob et al., 1989; Stoupel et al., 1989a; see also Stoupel, 1986, 1990; Stoupel and Ashkenazi, 1989; Stoupel and Shimshoni, 1988; Stoupel et al., 1988, 1989b, 1990). The availability of truly unobtrusive ambulatory monitoring hardware combined with chronobiologic software (Halberg et al., 1988) allows the investigation of any effects of cosmic drummers upon our physiology as well as upon diverse human pathology.

Apart from physiological monitoring, there is the as-yet unsupported possibility that satellites placed near the sun may serve to pick up changes in the Bz component of IMF that could prompt a timely warning for those at high risk of developing some of the conditions investigated by Breus et al. (1989) (by the study of calls for an ambulance). These conditions vary from cardiovascular disease to epilepsy or to traumatic injury sustained in or out of vehicles. In all these conditions, it seems reasonable, if not to shield, then to optimize the pineal function if it is the transducer of an undesirable effect of a magnetic storm or substorm. It also seems reasonable to optimize the patient's environment, notably critical care units, from the viewpoint of physical, psychological and social loads. Beyond these concerns, the dose and timing of any antiarrhythmic, antianginal or antiepileptic drugs taken by the patient may be modified. In turning from a physical to a physiological monitoring system based on variables such as blood pressure and heart rate, the large circadian changes that occur each day, even in recumbency, must be taken into account (Halberg et al., 1988), apart from any known environmental influences. It seems simpler to issue the warning from a satellite near the sun, if changes that may pose a risk on earth may have a latency of up to 5 hours, as may be the case for changes in solar wind vs. the K index. This possibility remains to be demonstrated for the case of magnetic storms. If a warning should be practical, there could be an interplanetary report together with the weather report.

Many authors, following the pioneering studies of Peterson (1937), continue to be concerned with weather and human morbidity and mortality, with focus on myocardial infarction, among many other conditions (Cech et al., 1979a and b; Changon et al., 1984; De Rudder, 1952; Driscoll, 1971; Julien, 1985; Larcon et al., 1983; Miric et al., 1989a-c; States, 1977). The relations between the weather and magnetic substorms and storms and between solar wind and human birth rate (Randall, 1990), presumably involving the pineal, remain topics of interest not only to meteorologists, but to the biomedical community as well. Randall emphasizes that at high latitudes, prominent circasemiannual rhythms are found in plasma melatonin with equinoctial troughs and solstitial peaks. He correlates these observations with the magnetic disturbance induced by the solar wind, which is most pronounced in the auroral zones where the corpuscular radiation enters the atmosphere. He also hints at a link between solar wind and the pineal.

In the data of Breus et al. (1989), we find a circasemiannual component for data on sunspots (P=0.027) and on the incidence of epilepsy (P=0.038) and perhaps stroke (P=0.088). The respective acrophases are very close (sunspots: -231°; epilepsy: -235°; strokes: -270°, with 360° representing 6 months). Randall suggests that sunshine and geomagnetic activity both act via the pineal. The pineal in turn may be responsible for a feedsideward sequence of inhibition, no-effect and stimulation of the gonad via the pituitary, as already demonstrated for the pituitary-adrenal modulation by the pineal (Sánchez et al., 1982; Halberg, 1983). The study of these putative endocrine mechanisms in a laboratory on the moon is indicated.

To conclude, chronophysiologic monitoring is of interest to space biology, and in particular for a lunar laboratory. From a basic viewpoint, the monitoring of physiologic variables such as blood pressure of a crew on the moon could examine the effects of an intermittent change of the extent of exposure to geomagnetism and interactions with microgravity. Blood pressure assessment could also be part and parcel of a telehygiene system concerning the astronauts' health, which constitutes the priority second to none. There may also be spinoffs for health on earth from the developments both of a cardiovascular telehygienic system and from an accompanying interplanetary Bz report based on satellite information that may accompany, as an entity in its own right, the regular weather report.

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