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OBITUARY

Pineal mythology and chronorisk: The Swan Song of Brunetto TARQUINI

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Brunetto Tarquini, head of Internal Medicine at the University of Florence, Italy, died at the peak of a productive career. A few days before his passing, his contributions to the 6th National Congress of the Italian Society for Chronobiology in Chianciano Terme—in the footsteps of the Roman poet Horace and the emperor Augustus (Rastrelli 1999; Soren and Romer 1999)—exuded scholarship, which we try to convey herein; on a trip after the meeting through his native countryside, Brunetto exuded friendship, for those living and also for those of quite a while ago.

Brunetto, who was born in Trequanda, near Siena, graduated in medicine from the University of Florence in 1963. He then went through the ranks, spending his entire professional career in Florence. In an earlier generation, Harvey Cushing visited Florence originally to enjoy Michelangelo's David and other works of art, but was pleased to encounter an outstanding medical atmosphere. Albeit with a lag in phase, Brunetto Tarquini further added greatly to the aura of Florentine medicine.

Here, Brunetto became professor of medical semeiotics and cardiology in 1981, and chief of an internal medicine department in 1990, a position he held until his untimely death. As director of the Inter-University Center for Clinical Chronobiology and as coordinator of a post-doctoral school in chronobiology, Brunetto influenced many young Italian physicians. He became the leader of a budding specialty of chronomedicine, coordinating an international group. His focus included temporal aspects of vascular diseases from womb-to-tomb as well as oncological risk factors. His research thus ranged from neonatology over neuroendocrinology to geriatrics, by studies on the pineal in particular, documenting the signature of heliogeomagnetic master switches for circulating human melatonin.

THE STORY BEHIND

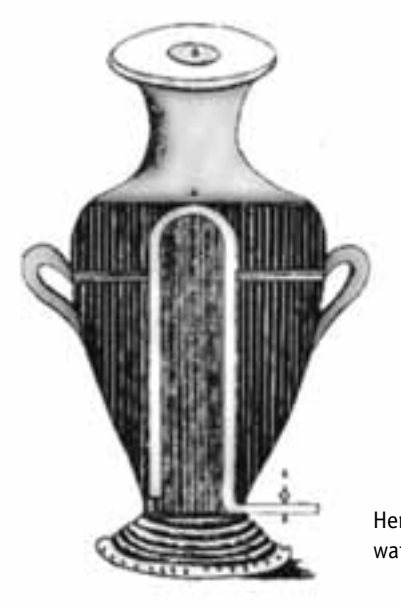
Chronobiologic contributions

Brunetto demonstrated the importance of timing the administration of drugs by showing that the same dose of bromocryptine had an effect at certain clock-hours, chosen as an approximation of circadian times, but not at another time (Figures 3 and 4 in Tarquini et al. 1980). Indeed, Brunetto remained on the frontiers of endocrinology. With his associates Federico Perfetto and Roberto Tarquini, he delved into the chronobiology of leptin (Tarquini et al. 1999a), dehydroepiandrosterone sulfate (Tarquini et al. 1997a), endothelin-1 (Tarquini et al. 1997b and c) as well as melatonin (Tarquini et al. 1997d, 1999b). For the human newborn, circadian and circannual leptin rhythms in cord blood were demonstrated, as were the unexpected role of the father and a possible relation to cholesterol metabolism. When many investigators chased putative circadian clocks, Brunetto's group discovered an about-half-weekly ET-1 rhythm. By sampling every 20 minutes for 24 hours, they made the added rare finding of an about-8-hourly periodicity (Simpson et al. 1990; Hildebrandt et al. 1998). Manfred Herold then showed that in health, the circaoctohoran ET-1 rhythm coexists with a 24-hourly cortisol pattern (Herold et al. 1998). One of Brunetto's many credits goes for providing the documentation of a half-yearly melatonin pattern by night (Tarquini et al. 1997d). Brunetto's textbook of internal medicine had won him the concorso of teaching (Tarquini 1983); the next edition, which Brunetto prepared, may well be another concorso, won posthumously.

History

Brunetto enjoyed history. This paper representing his scholarship traces interest in the pineal as the anatomical substrate of the soul, from the anima orbis ("world soul") to the Cartesian "mind," largely as presented by Brunetto, at the round table in Chianciano Terme two weeks before his death (hence his swan song). Starting long before Descartes (who is often misquoted as having indicated that the soul was housed in the pineal), Brunetto led us to the legendary Yellow Emperor (said to have reigned from 2697 B.C.–2597 B.C.) (Huang Ti Nei Ching Su Wen 1949). Other scholars of this time have failed to list the gland in their index. Brunetto also pointed out that in the Vedas, the religious teachings of India, the pineal was one of the chakras, the centers of vital energy. This chakra was the "door to perfect peace and harmony." It was not chance for Brunetto that in the Vedic pantheon one of the most potent deities was Varona, the god of the nocturnal sky, which directs the course of the sun.

The great anatomist and physiologist Herophilus of Alexandria (325–280 B.C.) taught in Alexandria during the reign of the first two Ptolemys. Herophilus studied first and foremost the brain, the eyes and the circulation; he described the nerves, the calamus scriptorius (or calamus herophilii), the occipital bone, the retina and the duodenum. In Chianciano Terme, Brunetto indicated with photographs that Herophilus may have been first to count, with an ingenious water clock, the beats of the pulse and thereby to diagnose even amorous passion. He found that Herophilus mentioned the pineal as an entity that is functionally involved in the coordination of the flow of thought (psychikon): as a sphincter between the ventricles of the brain and the nerves. Brunetto also cited Galen as indicating that the soul is in the center of the brain, in the pineal, rather than in the heart, as Aristotle claimed.



Herophilus water clock

Brunetto aligned the relatively recent concept of the soul, the Latin "anima," in the Confessions of St. Augustine (354–430 A.D.), with the Greek "psyche" and Hebrew "nephes": he explained that the latter means "life," including everything that contributes to life. Brunetto regarded it as possible that in Europe the teachings of the Vedas became known through the Templars, the monk-soldiers of St. Bernard, eventually mostly annihilated by Philip "the Beautiful" of France, except for those retained by the initiators of Freemasonry (Barber 1994; Demurger 1989; Partner 1982; Seward 1995). Brunetto reported parenthetically that it was indispensable for those entering into the order to have three horses, even if in a fight there were two riding a single horse. From the Templars may stem the kiss of the behind, which should excite or awaken the serpent Kundalini, a cosmic force which resides in the roots of the dorsal spine and in the sex glands, and which once awakened, reaches the pineal gland. Another secret of the Templars that Brunetto wanted to clar-

ify was a "third eye," namely that of a direct vision of time and space.

We can no longer ask Brunetto why he focused in such detail on the Templars. But in May 1987, in the ancient Templar house of Maggione in Poggibonsi, Tuscany, an international symposium was held on "The Templars, Myths and History" (I Templari, Mito e Storia). In 1999 as well, this title certainly applies to the pineal, to the point that a symposium proposed to an academy of science was denied because of an undue prominence of inspiration over perspiration. It must be remembered that in Italian, "storia" means not only "history" but also "story, tale." Conceivably, Brunetto raised the question "Quante storie per nulla" ("Much Ado about Nothing") also concerning some modern time structure (chronome)-unqualified research on melatonin.

In the 17th century, Rene Descartes (1596–1650), often cited erroneously to the contrary, maintained that the soul cannot be localized in any one part of the body, but he considered the pineal as the organ where the mind or anima (res cogitans) encounters the material, the fleeting mortal body (res extensa) ("There is a small gland in the brain, the pineal, in which the soul exercises its function in a more peculiar way than in all other parts": Descartes 1664/1972).

Against this long, mythical historical background the development of homeostatic scientific studies was delayed until the middle of the 18th century, when some studies contested the Cartesian view. Around the middle of the 17th century, Giovanni Battista Morgagni (1682–1771), the father of pathological anatomy, in "De sedibus" with his thorough postmortem examinations provides case histories for patients with "disturbances of the mind" as having anomalous, atrophic or calcified pineal glands. Indeed, the pineal has a particular propensity to calcify, as now documented with modern methods of imaging (Schorner et al. 1991; Kohli et al. 1992; Sandyk and Awerbuch 1991; Sandyk 1993). The calcification begins by the deposition of hydroxylapatite in pineal cells. The concretions, the acerbuli or the sand of the brain, are eventually expelled into intercellular space, where they form aggregates. The calcification of the pineal had different interpretations. The then-leading endocrinologist Nicola Pende, following up on Morgagni, maintained correlations of the pineal with "psychosexual alterations" including sadism, masochism, homosexuality and satyriasis. In the following century, other scholars like Thomas Arnold (1795-1842) make the same observation as Morgagni and diffuse the conviction that madness can be tied to the presence of an abnormal pineal gland.

In the last years of the 19th century, the first clinical cases of affections of pineal origin were reported. The anatomists of this time, as did the clinicians based on morphologic and comparative studies, regarded the pineal as a vestigial organ, biologically redundant. Some of those who more recently assessed the degree of calcification in the pineal by computerized tomography, have correlated this degree of calcification with a reduced production of melatonin, with alterations of sleep-wakefulness and tiredness during the day: but this was not found for 6-sulfatoxymelatonin on a small sample (Bojkowski and Arendt 1990). The pineal has been studied for a possible involvement in multiple sclerosis (Sandyk and Awerbuch 1992, 1994): a point of interest from a geophysical viewpoint (Resch 1995), in schizophrenia onset (Sandyk 1992a), and, more generally (Sandyk 1992b, 1993), in bipolar emotional disease (Sandyk and Pardeshi 1990) and in psychiatric illness overall (Sandyk and Awerbuch 1993).

The last 40 years

By contrast to the long, anecdotal history of the pineal, the history of a chemically defined entity is recent. Lerner discovered melatonin, an indole derived from 5-hydroxytryptamine, as the major, but not the sole secretion of the pineal, as recently as 1958. For the subsequent first 20 years, the pineal remained in obscurity (Brunetto points out that this was its natural environment!). It was catalogued as a neurochemical fossil, only to gain worldwide fame almost immediately thereafter, not so much because of the progress made in the discovery of the growing importance of the photofraction in agriculture but as a public response to the many hypotheses in experimental physiopathology about the critical properties of melatonin. From the end of the 1970s on to the first years of the 1990s, the pineal came to be resuscitated as an omnipotent, oncostatic organ, a proposition that had been made in Vienna in the pre-melatonin era (Engel and Bergmann 1952). Melatonin also became the pill for eternal youth, even if today aging, rather than representing a hope, constitutes more of a menace, as Brunetto put it, and in private he added, except for a good wine which improves with age.

Embryologically derived from the ependyma, which covers the ceiling of the third ventricle, the pineal or epiphesis, also called the penis of the brain, remains an ontogenetically very old organ, a member in the family of circumventricular secretory organs, which include the subcommisural organ (SCO), the subfornical organ (SFO), the organum vasculosum of the lamina terminalis (OVLT), the ependyma of the median eminence, and at the posterior border of the ceiling of the fourth ventricle, the area postrema. These organs, described also as the "windows of the brain," with the exception of the SCO, are areas which miss a blood-brain barrier. Their functions are not known with certainty. Along an evolutionary

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scale these organs could be involved in the metabolism of fluids, osmolality and electrolyte transport. Melatonin is indeed found in insects (Wetterberg et al. 1990) and unicells (Balzer and Fuhrberg 1996).

In the 1960s, Farrell postulated a hormone of pineal origin, adrenocortical glomerulotropin or briefly glomerulotropin, that coordinates the glomerulosa of the adrenal cortex, which produces aldosterone. The biosynthesis of aldosterone in the glomerulosa is influenced by a number of factors, notably by the octapeptide angiotensin II (Aguilera 1993; cf. also Franchimont 1964; Haulica et al. 1981; Damian, 1989). In some amphibians and some fishes, the pineal cells have characteristic photoreceptors with photosensitivity and electrical activity suggestive of a "third eye." In birds and reptiles, in addition to photoreception, there is a secretory function which becomes more pronounced in higher vertebrates. The vascularization of the pineal is rich, when viewed in relation to the amount of tissue. After the kidney, Brunetto regarded the pineal as the second most irrigated organ. This constitutes certainly a biological paradox, if the pineal is a redundant vestigial organ.

The pineal is innervated by post-ganglionic fibers that derive from the sympathetic ganglion and are found along the great vein of Galen. The sympathetic nervous input into the pineal is coordinated by impulses from the suprachiasmatic nuclei, which in turn are innervated directly from the retinal hypothalamic tract. Today, many investigators explore the potential role of melatonin beside that in oncology and geriatrics, in the treatment of many psychiatric conditions, including depression, bipolar manic-depressive illness, schizophrenia and Seasonal Affective Disorder, SAD. With SAD and its geographic distribution, Brunetto's scholarship concluded the foregoing broad perspective of the pineal from thousands of years ago to the future in which his data led to the recognition of the signature of geo- and heliomagnetics in the circulating melatonin concentration of his patients (Tarquini et al. 1997d).

Politics

Brunetto was fond of history beyond the boundaries of science. On the last day of our recent visit with him, he wanted us to dine in Macchiavelli's house; on the previous morning, after we saw, at least from a distance, his birthplace, we did go by the home of St. Roberto Bellarmino. Brunetto explained that Bellarmino was not Galileo's enemy and did all he could do to save him, but Galileo wanted to be crucified (i.e., arrested).

From clock to time structure (chronome).

Brunetto Tarquini's greatest contribution is chronorisk (Tarquini et al. 1979a and b; Cornélissen et al. 1999). In 1979, Brunetto assayed prolactin in serum obtained at six consecutive 4-hourly intervals from 22 women with fibrocystic mastopathy and 18 clinically healthy women (controls). He demonstrated a statistically significant circadian rhythm by population-mean cosinor for both groups. In the group with fibrocystic mastopathy, as compared to the controls, the circadian amplitude was only slightly higher when summarized in original values and slightly lower in relative terms, as percent of rhythm-adjusted mean or MESOR. These differences were not statistically significant ($P>0.05$). Nearly identical in the two groups was the rhythm's timing, assessed by fitting a 24-hour cosine curve to the data to obtain an acrophase estimate. For the group with fibrocystic mastopathy and the controls, the point estimates of the acrophase were nearly the same at -18 and -26 degrees from local midnight (01:12 and 01:44, since 360 degrees are equated to 24 hours) with the 95 confidence intervals extending from +4 (-356) to -38 degrees and from -6 to -47 degrees, respectively. A MESOR test established a MESOR-hyperprolactinemia in patients with fibrocystic mastopathy who, as a group, represent a population differing from the clinically healthy control subjects ($P<0.001$). To the clinician in medical practice, group tolerance intervals (chronodesms) were provided. These allowed a first interpretation (against a group reference interval) of prolactin concentrations in single rhythm-qualified samples (to be assessed eventually, whenever warranted, against individualized reference standards.

The biologic year in the clinic.

Brunetto summarized and concluded an observation that prompted him to consider chronorisk thus: "Although different women were sampled at different times of the year, a circannual rhythm of serum prolactin could be described for healthy women. For analysis by the single cosinor method, the MESOR from a given subject, sampled only six times at consecutive 4-hour intervals, was regarded as a serially independent sample and was assigned to the sampling date. A least-squares fit of a 365.25-day cosine curve to the MESORs of serum prolactin from the group of healthy women allowed the rejection of the zero (circannual) amplitude hypothesis. With the same sampling schedule, a circannual rhythm was not detected (i.e., the zero circannual amplitude hypothesis could not be rejected) for prolactin in serum from the group of women with fibrocystic mastopathy. The risk of breast cancer may increase as the extent of predictable circannual variation decreases. In this context and/or others, circannual rhythm characteristics occasionally may constitute a more sensitive index than circadian ones. Such possibilities await further scrutiny (Tarquini et al. 1979b)."

Confirmation and extension.

In a follow-up work, the about-yearly variations of prolactin and TSH were found to differ between groups of clinically healthy women at high vs. low familial risk of developing breast cancer, when their circadian rhythm did not show any statistically significant difference (Halberg et al. 1981). The circannual amplitude of circulating prolactin decreased and that of TSH increased with increasing familial breast cancer risk. These findings are in keeping with the suggestion that increased risk-associated circannual changes can precede those in the circadian system. A third related study took place in the Channel Islands (Bulbrook et al. 1987). Clinically healthy women had a sample of blood drawn and then stored until a later time when the presence or absence of breast cancer was determined. At that time, retrospectively, two groups could be formed, one of women who did and the other of those who did not develop breast cancer in the interim. In each group, various women were sampled in different seasons. To each of the series that were serially independent as to subjects, a one-year cosine curve was fitted. Those who did not have cancer yielded a statistically highly significant circannual prolactin rhythm, while this rhythm was not found in women actually documented as having subsequently developed breast cancer (Bulbrook et al. 1987).

The risk of developing breast cancer may thus be assessed by sampling blood repeatedly throughout the year. While sampling every 20 minutes for 24 hours 4 times a year, exploring several components in the spectral element of a variable's time structure, its chronome, was sufficient to detect differences among small groups, the most cost-effective scheme of sampling as yet will have to be established for individuals in order to detect an elevated familial risk of breast cancer as it is associated with a damping of the circannual amplitude of prolactin and an increase in the circannual amplitude of TSH. These findings were evident in the circulation of women with fibrocystic mastopathy, a putative high risk group at the time of study and validated to be such a group by the outcomes already discussed in women with a positive vs. negative family history of breast cancer (Halberg et al. 1981) or with and without actual cancer (Bulbrook et al. 1987).

Brunetto's findings were based on 6 consecutive 4-hourly samplings from the women he studied. Related observations that followed, on women with a positive vs. negative family history of breast cancer, not only as noted, were done at 20-minute intervals for 24 hours with serially dependent sampling in the four seasons, but also related to three age groups and in the two groups of menstruating women, the effect of circatrigintan stage was also explored (Halberg et al. 1981). Thus, the (age) trend as well as a more complete rhythmic element of the chronome were both explored (Halberg et al. 1981), yet even this relatively thorough rhythm exploration remains incomplete. Neither circaseptans nor about 10.5-year and 21-year changes were considered, yet in the interim, we learned that these can also have profound influences. Thus, more work remains to be done on the two groups that differed in the circannual amplitude of two endocrine variables.

But the remaining work is relatively simple as compared to that carried out earlier (Halberg et al. 1981). It was costly to detect circannual damping of the prolactin variation and amplification of the TSH changes along the scale of the year in the group with a positive family history. The critical confirmation as the third line of evidence came from studies on the Channel Islands reinforcing the original work in Florence, Italy, and its extension to Japan and the USA, cost-effectively. A single sample of blood had been drawn from women and stored until much later, when the women could be separated into two groups who had or had not developed breast cancer in the interim. As noted, when the endocrine data for prolactin were analyzed for each group, that with vs. that without cancer, a circannual rhythm of circulating prolactin was detected only in the group of patients without cancer, on the basis of a single sample, a cost-effective result in research, awaiting transfer into the clinic, as soon as the minimal sampling requirements for an individualized assessment have been established and the cost-effectiveness of this kind of risk detection vs. the use of multiple hormonal markers in single time-specified spotchecks on blood (Halberg et al. 1981) has also been scrutinized.

Chronorisk should be at the frontier of discussions, such as the 27th Bethesda Conference of the American College of Cardiology, on matching the intensity of risk factor management with the hazard of catastrophic events (Fuster and Pearson 1995).

We can do little about age, male gender, positive family history of high blood pressure and/or other vascular disease, socioeconomic status or, to touch upon legitimate (Cotton et al. 1972; Lesko et al. 1993; Herrera et al. 1995; Schnohr et al. 1995) even if still light-hearted concerns, baldness. We are helpless in confronting death, were it not that we try to implement what Brunetto wanted to do. Let us work in his memory, so that his legacy helps innumerable others who may be spared long, crippling and expensive illnesses, by our enabling them to detect and act on reducing chronorisk (Fossel, 1998; Cornélissen et al., 1999). We may call blood pressure overswinging an asymptomatic disease risk syndrome, predisease,

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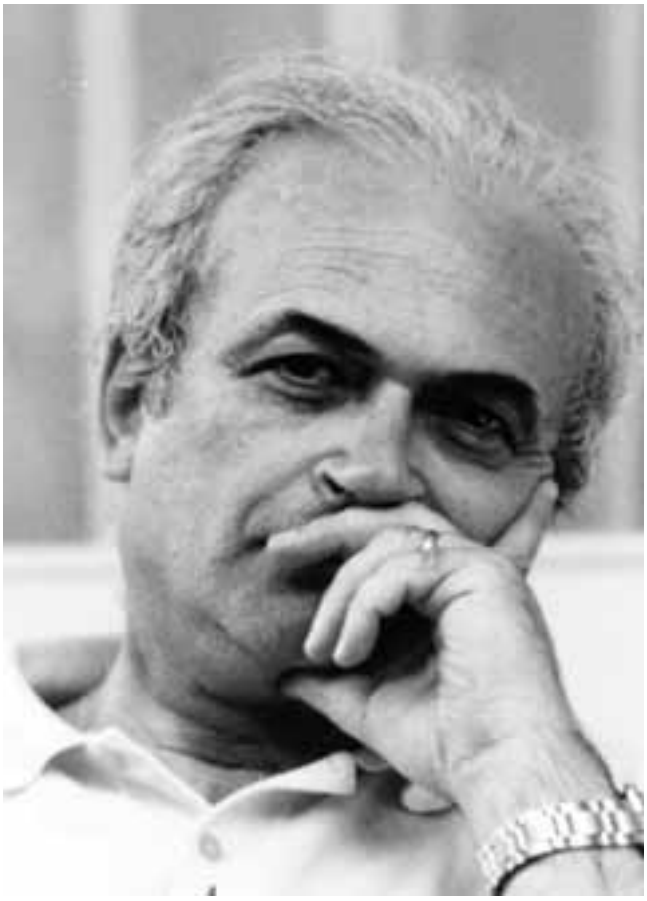

chronoprotopathology or any other name. What is important is that we act in a timely way for pre-habilitation (Cornélissen et al. 1999), rather than wait for the need for rehabilitation.

The friend and clinician.

Brunetto was a good internist, on himself as on others. He realized his prognosis once the diagnosis was made and was at peace with himself. We welcome that he did not suffer again for a long time, as he had earlier in the year. Good clinicians can be outstanding in one or another area. Brunetto was outstanding in all the areas he touched on. There are generous people, but few are competent academicians. Brunetto's generosity matched his scholarship. He offered all he had, whether data, scientific credit or material goods, without quid pro quo.

Brunetto always referred to a "Maestro." As we told him in public at the meeting in Chianciano Terme, he had become the maestro of many of us in a relatively short span of time. Some initiatives of picking topics for joint research may have been ours a long time ago; for the last years many were his, and we were happy to follow his lead.

Brunetto's thorough planning and data collection enabled analyses separately for each clock-hour, to show that melatonin responds to two master switches, one light by day, the other probably geomagnetics by night (Tarquini et al. 1997d; Halberg and Cornélissen 1998), with a half-yearly signature pointed out by Armin Grafe (1958).

Babies and the biologic week.

Brunetto's studies in Florence, Italy, coordinated with others in Brno, Czech Republic; Minneapolis and St. Paul, Minnesota, USA; and Moscow, Russia; also extended focus from circadians to about-weekly (circaseptan) changes in the human neonatal blood pressure and heart rate, showing that the circaseptan predominates over the circadian by a larger amplitude during most of the first month of life. The circadian rhythm in blood pressure showed initially an association of a positive family history of high blood pressure and/or other vascular diseases with a large circadian blood pressure amplitude. After several years with such findings on over 150 babies, the statistically significant association could not be reproduced. After every other avenue to account for this change by the medical or other treatment of the pregnant woman and/or the baby and/or by its environment was exhausted, changes in the remote physical environment were considered. An association of heart rate variability with solar cycle stage, gauged by Wolf number was found (Halberg and Cornélissen 1998). For chronomedicine and chronoepidemiology each to become a field sui generis, womb-to-tomb monitoring covering the changes with 10.5-year Schwabe and 21-year Hale cycles will be essential, at least on a few test pilots. In a day and age when we continuously monitor garages to prevent theft or rape, or supermarkets to catch shoplifters, why not monitor vital signs to detect earliest changes associated with disease risk elevation, in order to be able to act in time for prevention. Brunetto taught us that this should be done.

Asked what was his greatest contribution to science, Sir Humphry Davy named Michael Faraday. If the eldest among us is asked what his possible contribution to clinical medicine was, he can likewise name Maestro Brunetto Tarquini. Brunetto lives in spirit with those who try to replace rehabilitation (before as well as after the fact of chronic disease) with pre-habilitation in the face of chronorisk. Brunetto will be with those who try to replace a single-sample guesswork by time series analysis. He was concerned with us and with Earl Bakken's health-related quality of life (Bakken 1998; Cornélissen et al. 1999), about a budding chronobioethic. We can try to derive clues from today's ontogeny and phylogeny about the origins of life and the cosmos of that time. Does the prominence of circaseptans over circadians in Brunetto's data on newborns' blood pressure suggest that life locked-into the (last prominent) about 7-day harmonic of the planetary geomagnetic disturbance, Kp, spectrum. An answer in the affirmative makes sense for those life forms that may have developed far away from the

daily alternation of light and darkness which characterizes the surface of the earth. The origins of human and crayfish life (Fanjul Moles et al. 1998) may lead us to the bottom of the sea, wherever early in ontogeny, circaseptans are more prominent than circadians. But we must not generalize. Cyanobacteria that presumably have been around for as long as there has been oxygen on earth, seem to have a more prominent circadian, accompanied by a lesser about-weekly component (Halberg and Cornélissen 1998), insofar as one can speculate from extremely limited data.

Whatever our origin, Brunetto strived for more than existence as a link in a food chain. In finding the biological week in the human newborn, he tracked biology as it may have entered religious rites (Burkert 1996). On the trip over Montepulciano toward Siena, he volunteered his faith in a better world prompted by too much suffering he encountered on earth. Those of us who are still around down here plan to continue what we began with you, Maestro Brunetto.

A lively debate in the French Academy of Medicine (David 1998; Tubiana 1998) revolves around the advocacy by the legal profession of "precaution," i.e., governmental preventive measures at a time when as yet all the necessary rigorous evidence for the need of action is not yet in the hand of the medical profession. This debate comes to mind in considering action with respect to asymptomatic risk elevations. Circadian overswinging of the blood pressure, CHAT (Circadian Hyper-Amplitude-Tension), is one such syndrome (Halberg et al. 1998; Otsuka 1998). A reduced standard deviation of R-R intervals in the ECG is a CAHRV (Chronome Alteration of Heart Rate Variability), another indication of a high disease risk (Cornélissen et al. 1990; Otsuka 1998). The cost-benefit ratio from detecting CHAT and CAHRV seems most favorable for missions in space. CHAT detection in particular can help avoid the biomedical equivalent of the Challenger disaster. Industry may first satisfy the needs of health care in space away from hospitals on earth to develop a system of telehygiene that can become most helpful by instrumented self-help on earth.

With this goal in mind and with your evidence in hand, we respond today to your fax of January 19, 1990, which read: "ho voluto informarti per primo dell'esito del concorso ... *abbiamo vinto tu ed io* ... Brunetto"

Carissimo Brunetto, con infinita gratitudine, we and many others owe you much. You won, in all of the concorsos we face in life. You won the greatest concorso of all, far beyond that regarding academics: you won that of humility, being able to deprecate yourself. You won the concorso of basic science documenting the master switch of helio- and geomagnetism, complementing that of visible light. This invisible switch acts, as your data have shown, at night, in the absence of sunlight and heat; its effects may be less tangible, but perhaps no less important. Let us find out more about them on earth and wherever, with thanks for your melatonin studies (Tarquini et al. 1997d) humans venture into space (Halberg and Cornélissen 1998).

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