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Chronorisk/Circadian-Circannual (Macey, 1994):

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Times of high susceptibility predictable as the stages of rhythms, chaos and trends, e.g, with age, constellations among internal and/or external cycles in etiopathogenetically relevant variables, leading to the coincidence of peaks in potentially harmful and troughs in potentially protective stages, to the point that a disease or even a catastrophic event, such as sudden death, may ensue.

Chronorisk (1-3) depends critically on the organism, as shown in the laboratory, insofar as the same stimulus of the same intensity or in the same dose can tip the scale between death and survival, as a function solely of when it is administered (4-6). Such experiments with physical or biological stimuli have led to the concept of the (hours, seasons, and, more generally, the) times of changing resistance. When chronorisk is elevated by altered relations within the chronome(s) and in chronome(s) relations to the schedules (chronomes) of the environment, death can ensue, as it does in the laboratory—within seconds, minutes, hours or months, depending on the kind and intensity (dose) of the stimulus (such as audiogenic noise, ouabain or ethanol, endotoxins, dimethylbenzanthracene or X-irradiation).

Under standardized conditions outcomes are inferentially and statistically predictable in the experimental animal laboratory, barring only the effect of storms in space. When coordinated in time and in relative prominence, these rhythms and trends provide a shield against threats such as multiple disease risks, whether the risks are generated internally or externally. Rhythm and/or trend alteration or the failure of the organism to properly coordinate its structure in time may bring about weak spots through which the multiple disease risks can penetrate and affect the host. A better understanding of our structure in time may allow us to properly manipulate rhythms and the broader chronomes of relevant variables in order to enhance our protection against environmental threats, including sudden death or events such as strokes and myocardial infarctions.

Rhythm assessment, beyond the computation of a mean value, provides valuable information concerning chronorisk. For instance, an increased incidence combined with an amplified, phase-shifted circadian rhythm of premature ventricular beats in a 24-hour electrocardiogram performed after a myocardial infarction characterizes patients who die suddenly within 5 years as compared to those who survive (3). A rather complete chronome has been mapped to characterize the incidence of sudden infant death syndrome (SIDS) (7): there is a statistically highly significant difference of over one month in the age of peak incidence of SIDS vs. infant deaths from all other recorded causes, suggesting that an age of higher susceptibility for SIDS may be programmed congenitally. Prominent about-10-yearly, about-yearly, about-weekly, about-half-weekly and about-daily changes in the incidence of SIDS suggest that the ensemble of temporal features leading to SIDS may constitute an inopportune set of phase and amplitude relations among genetically programmed multifrequency rhythms and age trends (7). Similar patterns are found for the incidence of adult sudden death, myocardial infarction and stroke, among other conditions.

The increased incidence of myocardial infarctions and of other vascular diseases in the morning has been temporally, albeit not causally, associated with the morning increase in blood pressure and in platelet aggregability, concentrations of coagulant factors and blood viscosity, and the concomitant decrease in fibrinolytic activity, producing a state of hypercoagulability (8). About half-weekly and about-weekly rhythms have also been demonstrated in a measure of platelet viability, glutathione content in platelet-rich plasma stored in vitro (9). The importance of circasemiseptans in relation to the circulation is revealed by their demonstration in the beating of single cardiac cells in vitro (10). In vivo, blood pressure and heart rate free-run for several months under conditions of social isolation in a cave and afterward (11).

The phase relations between the incidence of several cerebrocardiovascular events and prominent rhythms characterizing physiologic variables have been further examined, beyond the circadian system. Circaseptan and circannual periodic components of blood pressure, await further mapping with cholesterol, triglycerides, catecholamines and aspects of vascular tone and blood clotting for a further understanding of underlying mechanisms. Cholesterol and triglycerides exhibit circannual, circaseptan as well as circadian variations (12).

Physiologic monitoring combined with chronobiologic analysis can recognize the presence of a heightened vascular disease risk, e.g., by an elevated circadian amplitude of blood pressure, already at birth (13, 14) and in adolescence (15), yet the extent of about 10-yearly modulations, the presence of which has been ascertained, remains to be thoroughly mapped. In adults, an elevated circadian amplitude of blood pressure is associated with an increased left ventricular mass index and precedes the occurrence of MESOR-hypertension (16). The circannual amplitude of diastolic blood pressure, assessed longitudinally by several 24-hour profiles of clinically healthy women on two continents (Minnesota, USA, and Kyushu, Japan), correlates negatively with the familial and personal risk of developing high blood pressure or related diseases later in life, as does the amplitude of the hormone aldosterone (17). The circannual amplitude of aldosterone correlates negatively with the circadian MESOR of diastolic blood pressure as well as with the questionnaire-derived cardiovascular disease risk index. Discrimination and classification techniques applied to these data have singled out aldosterone as a classifier of cardiovascular disease risk, a finding qualified by the circannual stage-dependence of the discriminating power of aldosterone as such a classifier (18)

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