LETTER

Rütger Wever: An Appreciation

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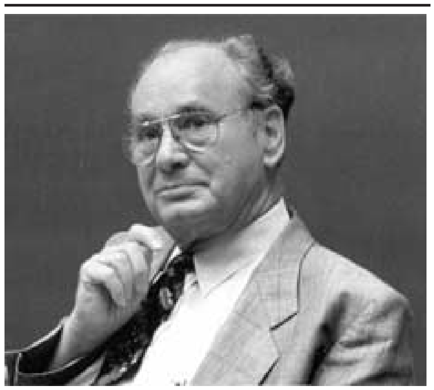
The Andechs bunker, where the first extensive human experiments in temporal isolation were carried out, has become history. Jürgen Aschoff himself was the first free-running subject, and Rütger Wever his observer. At the age of 82, Wever lives on a hill halfway between the cloister Andechs (of the famous beer) and the cloistered Max-Planck-Institut für Verhaltensphysiologie, the famous European center for biological rhythms research. A group of former colleagues gathered in July 2005 to render homage to this scientist's remarkable oeuvre. They wrote this appreciation, knowing well that many subsequent contributors to the field are omitted by focusing on Wever's research.



The brief overview of his achievements below should remind the younger generation of one of the great pioneers of human circadian biology. Rütger Wever's humility and reticence have led to a certain neglect in being cited for the fundamental concepts he discovered and described. As a physicist, his approach was mathematical, his analyses stringent; as an experimentalist, he was a never-tiring, ever-curious collector of the myriad strange phenomena elicited by the particular conditions of temporal isolation. His was the energy and persistence that designed and carried out, alone or in collaboration, day and night from 1964 to 1989, 418 experiments in 447 human volunteers in the bunker under nearly every conceivable condition (211 free-running). He summarized his findings in a dense, carefully written book, *The Circadian System of Man* (Wever, 1979), with all the data laid out, actogram by actogram, drawn in the immediately recognizable Andechs format. A succinct overview is found in his last review article (Wever, 1992, in *Temporal Variations of the Cardiovascular System*, Schmidt et al., eds, Springer).

The first demonstration of a free-running endogenous circadian rhythm in humans was followed by many experiments to dissect out modifying factors. An innate component is important in determining that individual τ:τ remains similar when studied years later. Women have a shorter τ than do men, but they have a higher fraction of sleep (by ~90 min, rarely attained in the real world). The circadian period in temporal isolation shows the aftereffects of prior photoperiod, with τ shorter in spring and autumn than in summer and winter.

There has been much argument about whether the Andechs bunker experiments adequately examined light as a zeitgeber in humans. They did so. "Aschoff and Wever have . . . reported that the LD cycle was too

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weak a zeitgeber to entrain the circadian systems of man" (Czeisler et al., 1981, Photochem Photobiol 34:239). Careful reading of the actual experiments and their interpretation shows that Wever concluded in a more differentiated manner: "An absolute light-dark cycle [= without auxiliary reading lights] has been shown to be a much stronger zeitgeber than a relative light-dark cycle [= with auxiliary reading lights]" (Wever, 1979, p 184). After the discovery of suppression of melatonin by bright light in 1980, Wever enthusiastically took up the challenge to install in the bunker brighter lights (3000 lux) than had been previously used (300 lux). His results were unequivocal. He found a broader range of entrainment (3×) than with light of common intensities. In addition, other putative entraining stimuli were carefully investigated, whether social signals (gongs or instructions) or social contacts (more than 1 person in the bunker), as well as the effects of electromagnetic fields and melatonin.

It is interesting to realize that Wever predicted clinical applications such as increasing zeitgeber strength, whether social or photic, to elderly and ill patients: "one should consider installing a lounge with artificial bright light facilities in hospitals, where the patient can spend many hours. It is to be expected that such a type of bright light therapy will assist in improving the quality of life in these patients" (Wever, 1992, p 79).

Already in the 1960s, Wever developed mathematical models of the (human) circadian system and its behavior under the influence of light. These models integrate the tonic effects of light intensity and its 1st and 2nd time derivatives, hence the action of twilights, an area now under renewed investigation.

One of the most extraordinary studies initiated by Wever in Andechs consisted of circadian organization in free-running blind persons. Blind subjects showed abnormal entrainment at individually different phase positions, free-running or relatively coordinated rhythms. The findings laid the basis for conceptualizing all putative circadian sleep disturbances.

The observation that the sleep-wake cycle could develop much longer or shorter periodicities than the temperature rhythm, and thus show internal desynchronization, was an important discovery already in 1967, later replicated in other laboratories. The decision in 1974 to investigate sleep-EEG in free-running experiments in Andechs led to an entire new dimension of human chronobiology. It forced sleep researchers to recognize the importance of the 24-h day, within which the one-third portion that interested them is embedded. The results regarding sleep structure in free-running rhythms were discovered in parallel in Andechs and New York. The phenomenon of internal desynchronization allowed dissection of the dependence of sleep duration on circadian phase.

These data, and ideas originally formulated by Charmane Eastman and Alex Borbély at the Ringberg meeting in 1980 (where so many crucial and stimulating interactions in our field began), led to the theory of a single circadian pacemaker gating a behavioral sleep hourglass process as a predictive model for human sleep regulation. Wever talked about 2 oscillators, but he had already analyzed their individual characteristics. He recognized that "the temperature clock is about 12 times stronger than the sleep-wake clock" (Wever, 1992, p 37) and that the temperature rhythm is synchronized by light, whereas the sleep-wake rhythm is more sensitive to social cues. Wever's multioscillator concept regains pertinence in a molecular era where circadian clocks are found in every organ, perhaps in every cell.

Many of the experiments used a forced T-cycle (either constant or changing period). This allowed eduction of the wave form of the circadian temperature rhythm, the rest-activity cycle, and even of different performance measures, anticipating the data collected in different laboratories using forced desynchronization to separate out circadian- and sleep-wake–dependent components of any given variable. Wever clearly saw that the contribution of the rest-activity cycle has to be removed to evaluate the "pure" circadian component, either by constant behavioral routines or by spreading the behavioral variations equally over the circadian cycle.

For psychiatrists, 3 findings were important. The concept of abnormal synchronization between the circadian system and the sleep-wake or light-dark cycle was crucial in developing models to understand the cyclicity of affective disorders. Second, these ideas were supported by the finding that subjects with higher neuroticism scores showed higher rates of internal desynchronization. Third, the apparent paradox of better mood and well-being after sleep curtailment during internal desynchronization provided a model for the switch out of depression into mania. In the last years of the Andechs bunker, even depressive and sleep-disturbed patients were studied under free-running conditions.

We are grateful to have had the chance to work with Rütger Wever; his pioneering work on the human circadian clock has deeply influenced not only our subsequent research but also that of the entire field.