Chronobiology 1982-1983

E. Haus H. Kabat

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Preface

Chronobiology, the study of biologic time structure, is a new applied and basic science that is becoming internationally recognized and which is revealed as a fledgling discipline in transition. The facts presented in this volume indeed reflect the continued rapid development of this discipline with its own tools, methods, concepts and broad areas of application, exploiting a spectrum of rhythms with different frequencies. The inferential statistical analysis of rhythms, based on modern computer methods, has been shown to be an indispensable tool of many basic and applied chronobiologists. With such tools available, however, it is simpler and more efficient to extend the focus from the study of ultradian and circadian rhythms to the field of infradians with a frequency lower than 1 cycle in 28 h.

Notable exceptions notwithstanding, most research in clinical chronobiology has relied primarily or exclusively on traditional techniques for measuring blood pressure, heart rate and temperature, among other variables. However, reports based on automatic monitoring have begun to complement self-measurement for rhythm assessment, notably in chronopharmacology. The critical importance for chronobiology of automated data collection and data transfer have come clearly to the fore.

The importance of rhythms with several frequencies is best emphasized by the fact that many have been shown to account for the difference between life and death in response to the same agent, and even for the difference between an acceleration and retardation of cancerous growth as a function of timing. Certainly, a large difference in human toxicity of anticancer drugs has already been documented. Some of the rhythms with several frequencies, summarized in this book, are pertinent to the treatment of cancer. Host tolerance of toxic drugs undergoes about-weekly, about-monthly and about-yearly, as well as about-daily rhythms.

Marker rhythm characteristics were introduced at the XVth International Conference of the International Society for Chronobiology, (held in Minneapolis, Minnesota, Setpember 8–11, 1981) for the dual purpose of monitoring optimal times for treatment and for gauging its effects in cancer patients. Thus, today, one can tentatively suggest that for diurnally-active, nocturnally-resting subjects, the optimal (population-based) time to administer doxorubicin, based on endpoints is related to several marker rhythm variables. In clock-hours this occurs between 0145 and 0400, as judged by the depressed area (within the month following treatment) of the total leu-

kocyte count when the acrophase of this count, or that of neutrophils, platelets or urinary potassium excretion is used as reference. The corresponding gain (computed as excess toxicity resulting from treatment at the inopportune, instead of the optimal time) exceeds 28% in each case. Moreover, one can specify the best timing for the individual, i.e., doxorubicin treatment at ~9.5 h after the acrophase of the total leukocyte count, is the primary consideration if avoiding myelotoxicity. When cardiotoxicity is to be avoided, the tentative best treatment time is around 22 h after the heart rate acrophase. While this heart rate acrophase can be determined from self-measurements of pulse rate, denser data with much less interference, notably without interrupting sleep, is obtained when heart rate is monitored automatically. Moreover, data punching prior to analysis can thus be eliminated. Direct as-one-goes data storage on a floppy disk, allowing heart rate data to be transferred rapidly from the automatic recorder to a personal computer has been accomplished in the home of a patient with breast cancer, using a Nippon Colin (Komaki, Japan) monitor. Nevertheless, chronobiologic engineering for the cost-effective use of clinical and biochemical variables still has a long way to go; it will require the wedding of hardware and software for applications in clinical chronobiology to open new avenues for the prevention and treatment of major life-threatening and incapacitating diseases.

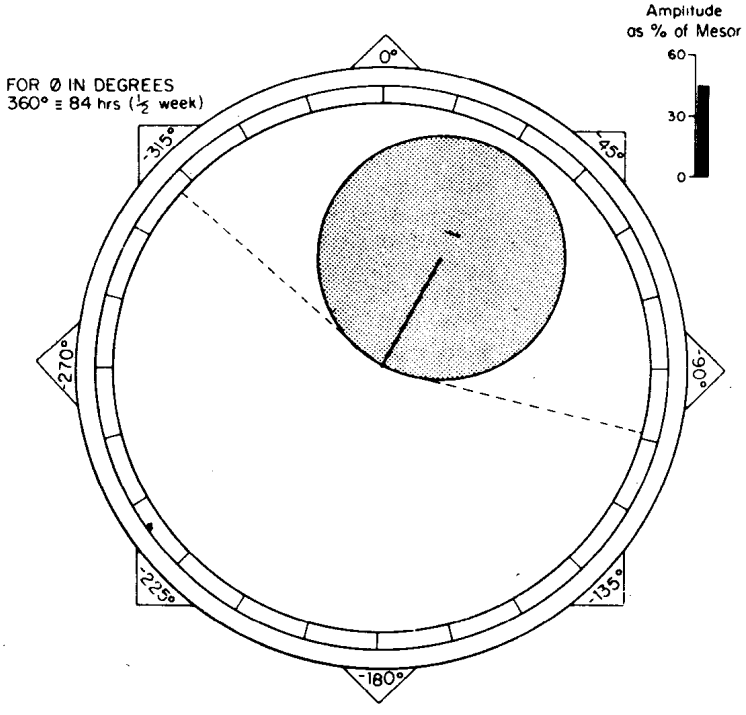
Chronobiology's major goals have not yet been reached; its rewards depend on chronobiologic engineering. This endeavor promises rewards even greater than those of genetic engineering, an optimistic view that stems from the ubiquity of rhythms with both genetic and environmental components. Genetic engineering can do something about the gene; chronobiology can address both the gene and the environment. By timing, work on basic problems becomes chronomolecular engineering.

Health can be gauged by quantifying rhythms. Rhythm parameters provide new endpoints for the definition of health and the recognition of disease. Chronobiologic methods also serve as a basis for recognizing risk and screening for disease, as well as adding timing to treatment dosage schedules. For the current treatment of cancer, however, a major immediate promise of chronobiologic technology lies in implantable programmable pumps with optimization by timing taken into account.

It is also important to realize that sources of major diseases of our civilization may be assessed, perhaps many decades before they occur, for states of heightened risk. Cost effective preventive medicine must endeavor to test, as early as possible, for the risk of various cancers, high blood pressure related diseases, and also chemical dependency, emotional depression and other conditions. Today, newborns are tested routinely, but only for relatively infrequently recurring conditions. If the results obtained in chronoepidemiologic studies can be validated in younger individuals (followed as a group), a predictive test, very early in life, for a heightened risk of developing a given condition can be applied to single out those individuals who may require preventive therapy, when such measures are available. When, as in the case of breast cancer, such measures are not yet known, the hormonal changes associated with heightened risk may point the way to a rational basis for developing novel preventive measures. In any event, individualization with time-specification of a measure allows one to dispense with the obligation to apply all preventive measures on a mass basis; instead, one can individualize them by rhythmometric criteria. Chronobiologic research provides such criteria as time-specified reference intervals for the clinical laboratory, which make the interpretation of any single laboratory determination on rhythmic variables more meaningful and cost effective.

From the viewpoint of basic biology, as well as in clinical perspective, focus is being redirected toward circaseptan (about 7-day) rhythms that have no known approximate match, i.e., no obviously prominent environmental counterpart. Reference is made in the book to the temperature compensation of the circaseptan period in a poikilotherm. Circaseptan organization has led us to postulate the process of an internal evolution as a basis for biological time structure. The latter is not merely a result of periodicities impinging on us from our environment. Evolution in the internal environment depended upon feed-sidewards in networks, which usually substitute for (oversimplified) feedbacks along axes. Apart from the evolutionary biologist's interest in circaseptan and circasemiseptan rhythms, however, the clinician can no longer question the importance of circaseptan rhythms; these rhythms are a determinant of sudden death (fig. 1).

Many of the chapters in this book add to the store of valuable chronobiologic facts. The new data represent an indispensable store of information for biologists dealing with corresponding time-varying functions. More and more endeavors will have to turn to the use of *p*-values



SINGLE COSINOR

P	No Obs	Percent Rhythm	Amplitude, % of mesor† (94 % CL)	Acrophase, degrees†† (94 % CL)
0.05	14	41	44 (1.18, 87.)	-28 (-311, -105)

P = probability of hypothesis: amplitude = 0; No Obs = number of observations; Percent Rhythm = percentage of variability accounted for by cosine curve; 94 % CL = 94 % confidence limits derived from cosinor ellipse.

† *mesor ≡ 100 %*
†† *from midnight Sunday to Monday (≡ 0°)*

FIGURE 1. About 3.5-day (circasemiseptan) rhythmic feature of sudden human death. Original data by Rabkin et al (3) who examined records of 3,983 men for sudden cardiac deaths. Sixty-three deaths occurred in the absence of information on previous *i*schemic *h*eart *d*isease (IHD), 89 in the presence of IHD. For the 63 deaths without IHD and for the total of sudden cardiac death, the original authors established differences by X^2 with a $p < .01$; they comment on the excess of sudden cardiac death on Monday. Myers and Devar (2) comment in turn on the role of a large consumption of alcohol on Saturdays. In Rabkin et al.'s data (3) a second peak on Thursdays is apparent to the naked eye. The frequency multiplication (doubling) of an internal circaseptan rhythm which is merely synchronized by the burden of returning to work on Mondays and influenced by other factors is a reasonable working hypothesis. Note that the best-fitting period is of 84 h (½ week) rather than 168 h (1 week) length. We are dealing with a frequency-doubled (circasemiseptan) change. This rhythm is apparent from the fact that the 95% confidence ellipse from the fitting of an 84-h cosine curve does not cover the center (pole) of the cosinor plot. This result of analysis is in keeping with much evidence on the ubiquity of circaseptan rhythms, their free-running in man, their relative temperature compensation in the springtail (discussed in this volume) and their frequency multiplication, e.g., in a fatal case of cardiac arrhythmia, studied after a triple coronary bypass operation (1). Apparently 7-day-synchronized circaseptan-rhythmic mortality has also been documented, by autocorrelations, for homicides, motor- and non-motor-vehicle accidents and suicides (4). p = probability of hypothesis; amplitude = 0; no obs = number of observations; percent rhythm = percentage of variability accounted for by cosine curve; 95% CL = 95% confidence limits derived from cosinor ellipse. † = mesor ≡ 100%; ff from midnight Sunday to Monday (≡ 0°).

to ascertain the likelihood of intended or other changes in rhythm characteristics of the given individual (rather than merely for distinguishing some groups under investigation).

The introduction to an earlier volume concluded with a hint of the need for measuring what is measurable and rendering measurable that which as yet is not. The biologist's and the physician's "meaningful" in 1984 includes a temporal perspective based on a growing number of facts.

Franz Halberg

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