Clinical Chronopharmacology
An Experimental Basis for Chronotherapy
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The practical significance of biological temporal structure is well illustrated by chronobiologic findings pertaining to the administration of medicines. Metabolic pathways are neither open with the same level of efficiency nor oriented continuously in the same direction (Reinberg 1974b, 1976a,b). The sensitivity of target systems to chemical substances varies rhythmically, too. New experimental methods and concepts have been developed to research, comprehend, and describe bioperiodic changes in drug effectiveness and tolerance. The major aim of clinical chronopharmacology is the optimization of therapeutic interventions. By manipulating therapeutic administrations as a function of the organism’s biological time structure, it is possible to enhance the desired and reduce the undesired effects of several types of medications.

Introduction
With reference to medical tradition, but not necessarily to scientific rationale, medicines are prescribed for specified clock hours. The timing of therapeutic measures today is related more frequently to psychosocial considerations, less frequently to empirical observations. Sometimes the homeostatic hypothesis is offered as the basis for a treatment schedule. Only occasionally, before the 1960’s, was an experiment designed to evaluate objectively, for a given agent, the advantage of a well-defined chronotherapy. In light of many new findings, it is now pertinent to reexamine the present-day rationale for administering treatments at particular times of the day and/or night.

The scheduling of treatments is based primarily upon prevailing scientific hypotheses as well as achieving patient compliance. With regard to the latter, involving psychosocial considerations, patients are instructed to ingest or inject prescribed medications at meal times with the hope that a high level of compliance will be attained. With regard to the former concern, the homeostatic hypothesis implies that the pharmacologic, therapeutic, and toxicologic effects of chemical substances should be the same, independent of the timing of treatment. Both desired and undesired effects of medications are expected to be identical no matter the hour, day, or month of administration. This hypothesis has been

Based on currently available data, the homeostatic philosophy of therapeutic management has to be viewed as obsolete and in some cases inappropriate or even dangerous. A chronobiologic approach often is indispensible for solving a set of therapeutic problems, including the reduction of undesired effects.

The belief that chronotherapeutics has important and practical application in medicine is not a recent one. In 1814 Julien Joseph Virey wrote that Thomas Sydenham, who based his judgment on empirical observations, recommended the narcotic opium (laudanum) be given in the late evening rather than in the morning to achieve best therapeutic effect. It was not until more than 150 years later that chronopharmacologic investigations of anesthetics, barbiturates, and narcotics on rats by Scheving et al. (1974), Nair (1974), and Bruguerolle et al. (1979) and on men by Fukami et al. (1970), Nicholson and Stone (1977), and Simpson et al. (1973) confirmed this empirical observation. Recognition must be given to Jores (1938), Möllerström (1953), and Menzel (1955); their pioneer work constitutes the foundation of today’s chronopharmacologic and chronotherapeutic studies. These investigators recognized 40 years ago that the bioperiodicities of human beings must be taken into account and, if need be, restructured when treating disease. Specific chronobiologic methods are now available to achieve these goals (Aschoff et al. 1975; Halberg 1960, 1969, 1975; Halberg et al. 1967, 1972; Haus et al. 1974; Philippines 1974; Reinberg 1971, 1974b, 1976a; Reinberg and Halberg 1971; Scheving et al. 1974; Sturtevant 1976; Reinberg and Smolensky 1982).

**Development of Clinical Chronopharmacology**

Modern chronopharmacology involves both the investigation of drug effects as a function of biological timing and the investigation of the effects of drugs on the characteristics of biological rhythms: period, $\tau$; acrophase, $\phi$; amplitude, $A$; and the rhythm-adjusted mean or mesor, $M$. Regular and thus predictable changes in biological susceptibility and response to a large variety of physical as well as chemical agents (including foods and drugs) are now viewed as rather common phenomena. This is true for both plants and animals (Haus et al. 1974; Reinberg 1974b; Reinberg and Halberg 1971; Scheving et al. 1974), including man. Experimental evidence of circadian (~24 hr), circamensual (~30 day), and circannual (~1 year) changes in human biological responses to various chemical and physical agents has been presented elsewhere in review papers (Halberg 1962, 1969; Halberg and Reinberg 1967; Halberg et al. 1967, 1969, 1972; Reinberg 1965, 1967, 1971, 1974a-c; Reinberg and Halberg 1971).

The findings of earlier chronobiologic studies led to concepts such as the hours of changing responsiveness (Halberg 1960, 1962, 1963; Reinberg 1965, 1967), chronopharmacology (Reinberg and Halberg 1971), chronosusceptibility (Reinberg 1967), chronotolerance (Halberg et al. 1977), as well as chronesthesy, chronopharmacokinetics, and chronergy (Reinberg 1976a; Reinberg et al. 1975) as depicted in Fig. 1. Recognizing that review papers have been published recently on this and related topics, the aim of this chapter is to provide illustrative examples of human circadian chronopharmacology and chronotherapy.

The objective demonstration of chronopharmacologic phenomena demands