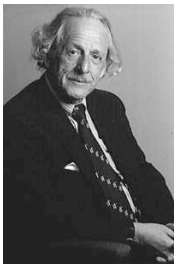
Essays of an Information Scientist: Science Literacy, Policy, Evaluation, and other Essays, Vol:11, p.7, 1988
Current Contents, #2, p.3-9, January 11, 1988



Current Comments®

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Chronobiology: An Internal Clock for All Seasons. Part 2. Current Research on Seasonal Affective Disorder and Phototherapy

Number 2 January 11, 1988

Using ISI® data, this essay (the second of two parts) discusses the most active research fronts in the field of chronobiology, the study of internal biological rhythms. Topics of interest to researchers include seasonal affective disorder (SAD), a condition brought about by the effect of light on the circadian rhythm, and phototherapy, the use of light to adjust biological clocks.

In Part 1 we discussed chronobiology, the study of internal biological clocks, and outlined its development as a distinct scientific discipline.[1] We now describe some of the current research under way in this field.

Trends in Chronobiology

In Figure 1 a historiograph showing a microhistory of the field since 1978 gives a clear indication of the increase in chronobiology research. Although it may appear that there has been a decline in research from 1985 to 1986, this is really just a consolidation; a glance at Table 1, which lists several 1986 *Science Citation Index®/Social Sciences Citation Index®* research fronts on chronobiology, shows that research on various aspects of biological rhythms continues at roughly the same pace it has for the past few years. The multidimensional-scaling map in Figure 2 shows the relationship between these fronts.

As is evident from the titles of these fronts, work in chronobiology is currently focusing not so much on how biological rhythms function but on how they malfunction. Many concern the consequences of rhythms that do not properly respond to or are out of phase with their synchronizers. One of these is the largest front in Table 1, entitled "Photoperiodic regulation of affective disorders and depression" (#86-0940). It is associated with 42 core papers and 338 published (citing) papers. Among the core papers are six articles by Colin S. Pittendrigh, Stanford University, California,[2-7] and two by Jürgen Aschoff, professor of physiology and director, Max Planck Institute for Behavioral Physiology, Seewiesen über Starnberg, Federal Republic of Germany (FRG).[8,9]

Front #86-0940 deals with the effects of light and temperature on biological rhythms in various organisms and how these environmental factors can both cause and be used to treat sleep disorders, depression, and other affective disorders. For instance, two core papers by Charles A. Czeisler, Laboratory of Human Chronophysiology, Department of Neurology, Montefiore Hospital, Bronx, New York, and the Sleep Research Center, Stanford University School of Medicine, and colleagues report the results of studies on the relationship between circadian rhythms and human sleep.[10,11] Incidentally, Czeisler and his work were featured in a recent *National Geographic* article on sleep.[12]

One of the core papers, published in 1980, shows that the duration of sleep and episodes such as the rapid-eye-movement (dreaming) phases were correlated with body temperature rhythms and not with the length of prior wakefulness.[10] The other, published two years later, discusses the effects that rotating shift work has on sleep and health. Czeisler and colleagues found that work schedules that continually violate the circadian rhythms

of workers reduce worker productivity, job satisfaction, and subjective health estimates and increase personnel turnover; work schedules that are in harmony with workers' circadian rhythms produce the opposite effects.[11]

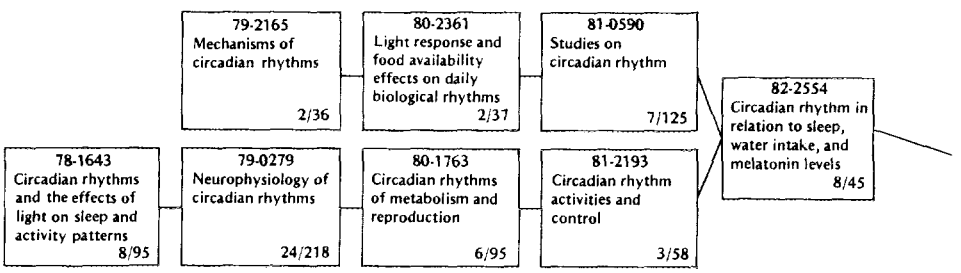
Another biological function that has been found to have a circadian rhythm in mammals is the secretion of melatonin, a hormone produced by the pineal gland that causes the pigment melanin to be concentrated in certain cells. Under normal conditions, melatonin secretion takes place almost exclusively during the nighttime hours and persists in a 24-hour rhythm even in constant darkness. The first report of an endogenously generated rhythm in the regulation of melatonin production was made by David C. Klein and Joan L. Weller in 1970, when they were at the Section on Physiological Controls, Laboratory of Biomedical Sciences, National Institute of Child Health and Human Development, Bethesda, Maryland.[13] This classic work has been cited over 465 times since then. In his *Citation Classic®* commentary, which appears in this issue of *Current Contents® /Life Sciences*, Klein notes that "the report has been frequently cited in part because it indicated that the [N-acetyltransferase activity that regulates melatonin production] was driven by an endogenous clock."[14]

In a core paper published in 1980, Alfred J. Lewy, then of the Clinical Psychobiology Branch, National Institute of Mental Health (NIMH), Bethesda, and colleagues found that bright artificial light suppresses the cycle of melatonin secretion in six normal human subjects, just as artificial light of less intensity does in other mammals.[15] This also established "that the human response to light is qualitatively similar to that of other mammals."

Another intriguing effect of bright artificial light is its role in the treatment of seasonal affective disorder (SAD), a recurrent depression that appears and disappears at the same time each year. In another paper that is core to front #86-0940, Lewy, currently of the Department of Psychiatry, Sleep and Mood Disorders Laboratory, Oregon Health Sciences University, Portland, and some of the colleagues he worked with in the melatonin study collaborated with Norman E. Rosenthal, NIMH, and others on a paper describing SAD and some preliminary results of the use of light in treating the condition.[16]

They studied 29 patients who suffered from depressions that were marked by overeating, oversleeping, a craving for carbohydrates, a decrease in physical activity, and difficulties at work and in interpersonal relationships. These depressions recurred each year at the same time (as summer changed to autumn) and improved at the same time each year (in the spring). Interestingly, depressed patients responded to traveling north or south in the winter: traveling south caused an amelioration in their symptoms, while traveling north exacerbated them. The authors conclude that the patients' illnesses were related to environmental factors—specifically, the number of daylight hours. They speculate that SAD may be a "pathologic manifestation of an [ancestral] seasonal rhythm," pointing out several similarities between patients suffering from SAD and hibernation in animals, such as increased sleep and appetite, decreased activity,

Figure 1: Historiograph tracing research on circadian rhythms in humans and animals from the 1978-1986 *SCI® /SSCI®*. The numbers of core/citing papers are indicated at the bottom of each box.



weight gain, and change in food preference.[16] Hibernation will be the subject of a future essay.

Rosenthal and colleagues have continued their research into SAD and light therapy and have arrived at several important findings. Concerning melatonin secretion, for example, Rosenthal and colleagues showed that while melatonin plays some role in the symptoms of SAD as well as in treatment of the condition, changes in the level of melatonin secretion are neither sufficient to cause SAD nor to relieve it.[17] Thus, according to Rosenthal and colleagues, the efficacy of phototherapy for SAD may not depend on how successfully it changes the pattern of melatonin secretion.[18] They also suggest that timing the application of phototherapy during a certain part of the day may not be critical to the success of the treatment,[18] although Lewy and colleagues found that phototherapy during the morning was more effective than the same therapy applied during the evening.[19] Rosenthal and colleagues have also shown that the antidepressant effects of light appear to be mediated by the eyes rather than the skin[20] and are not dependent on extending the length of the day.[21]

A front related to #86-0940 is entitled "Circadian pacemaker in pregnancy and depression" (#86-7831). It deals with some of the physiologic aspects of circadian rhythms and their relationship to various biological functions. It has 108 citing papers and 7 core papers, of which 4 are by Pittendrigh. Three are part of a five-part analysis of circadian rhythms in nocturnal rodents, published with coauthor Serge Daan, Zoological Laboratory, Groningen State University, The Netherlands.[22-24] The other reviews various properties of free-running circadian rhythms and environmental cues that force these cycles into the rhythm of the 24-hour light-dark cycle.[25] Also core to this front is a review by psychologists Benjamin Rusak, Dalhousie University, Halifax, Nova Scotia, Canada, and Irving Zucker, University of California, Berkeley, on the neurological basis for biological rhythms in various animals.[26] This classic paper has been cited over 450 times.

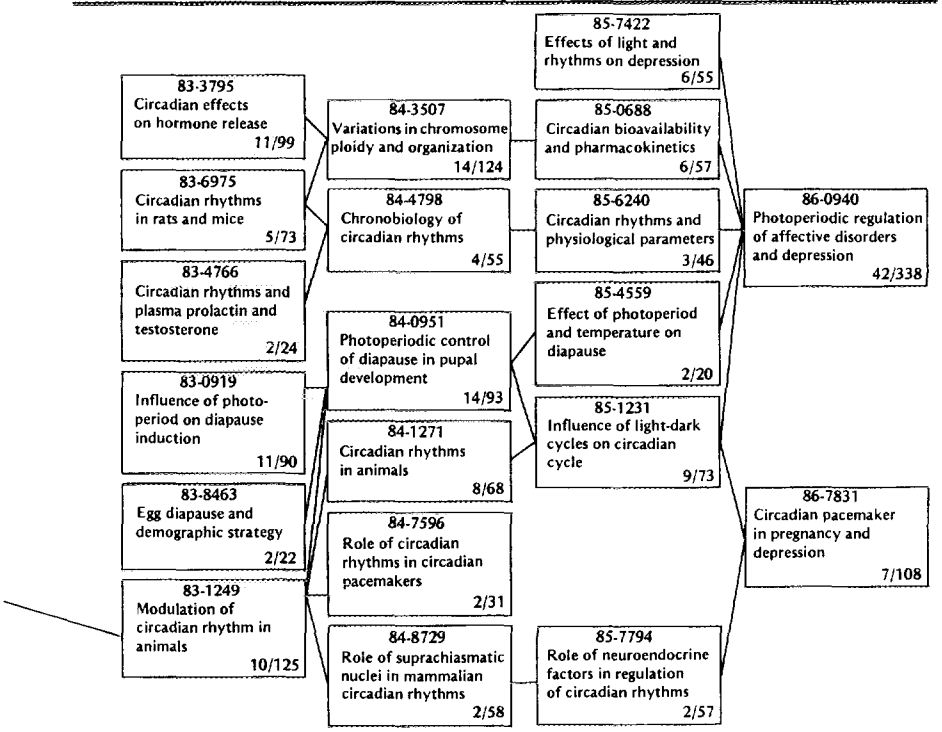


Table 1: Selected 1986 *SCI*® /*SSCI*® research fronts on various aspects of circadian rhythm, chronobiology, and biological clocks. A = number of core papers. B = number of citing papers. C = number of papers published in 1987 citing into this research front.

Number	Name	A	B	C
86-0940	Photoperiodic regulation of affective disorders and depression	42	338	228
86-1226	Thermoregulation and photoregulation effects on animal energetics	12	94	57
86-1278	Endocrine controls, breeding cycles, and seasonal changes in plasma levels	14	127	120
86-6416	Circadian seasonal variations of venous blood components in humans and mice	2	26	20
86-7831	Circadian pacemaker in pregnancy and depression	7	108	70
86-8092	Cellular circadian clocks	3	23	11

The biological rhythms of animals are also the focus of the front entitled "Thermoregulation and photoregulation effects on animal energetics" (#86-1226), with 94 papers published in 1986. Among the 12 core papers for this front is a 1970 article by Aschoff and H. Pohl, Max Planck Institute for Behavioral Physiology.[27] It discusses circadian rhythms in the metabolic rate of warm-blooded organisms. A core paper by zoologists Robert C. Lasiewski, UCLA, and William R. Dawson, University of Michigan, Ann Arbor, also discusses rhythmic variations in metabolic rate—specifically, in birds—and relates these to variations in body weight.[28]

A smaller front concerned with the mechanisms of biological rhythms in animals is called "Cellular circadian clocks" (#86-8092). It has 23 citing papers and 3 core papers—one by Pittendrigh on the internal clock that controls emergence from the pupal stage in fruit flies[29] and the other two by Hans-Georg Schweiger, Max Planck Institute for Cell Biology, Heidelberg, FRG.[30,31] Schweiger coauthored one with Manfred Schweiger, Institute for Biochemistry, Innsbruck University, Austria, on the functioning of the biological rhythms of unicellular organisms at the molecular level.[30] The other, coauthored with P. Dehm and S. Berger, Max Planck Institute for Cell Biology, discusses the conditions under which *Acetabularia* cells grow best in culture.[31]

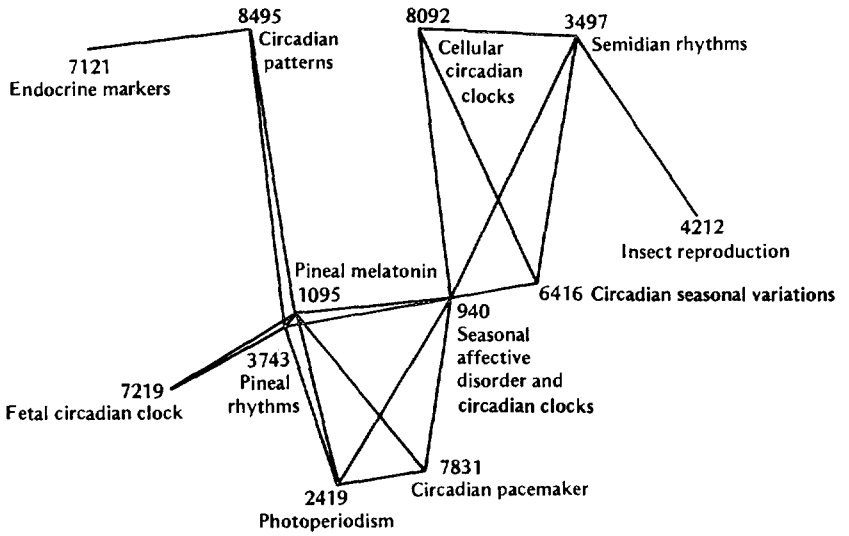
The front entitled "Circadian seasonal variations of venous blood components in humans and mice" (#86-6416) has 2 core papers and 26 citing papers. One of the core papers, by Erhard Haus and colleagues, Department of Pathology, St. Paul-Ramsey Medical Center, St. Paul, Minnesota, deals with the effects of biological rhythms on the components of the circulatory and immune systems.[32] The other, by Walter Nelson and Franz Halberg, Chronobiology Laboratories, Department of Laboratory Medicine and Pathology, University of Minnesota, and colleagues, reviews various methods for measuring the period of biological rhythms.[33]

Rhythms and Folklore

As evidenced by the research highlighted in this essay, the idea that the activities of organisms are regulated by internal timing mechanisms that are synchronized by environmental factors has been well established by scholarly investigations. Nevertheless, many popular notions concerning biological rhythms are still plentiful, often with little evidence to support them. Indeed, one such popular warping of chronobiology involves the use of what have been termed "biorhythms" by mystics and astrologers to forecast good or bad days or specific events in an individual's life, based solely on knowing the individual's birthday. However, as noted by Alain Reinberg, director of research, National Center of Scientific Research (CNRS), Paris, France, and Michael H. Smolensky, associate professor of environmental sciences, University of Texas Health Sciences Center, Houston, this is a "completely invalid and unacceptable definition" of the term, rendering its use by chronobiologists infrequent.[34]

Other popular beliefs surround rhythmic variations based on the phases of the moon. Although lunar phases are indeed correlated with some biological periodicities, such as menstruation in women[35] and metabolic and hormonal changes in salmon that regulate the fishes' reproductive process,[36]

Figure 2: Multidimensional-scaling map showing links between C1-level research fronts for the 1986 *SCI*® /*SSCI*® C2-level research front #86-0411 on circadian rhythms.



other associations between the moon and biologic events are less concrete.

For instance, one notion involves an association between the moon and fertility or romance. Several studies have found a weak, but definite, positive correlation between the phases of the moon and birthrates—i.e., births increase as the moon approaches fullness, peak when the moon is full, and decline thereafter, with the bottom of the curve occurring during the new-moon phase.[37-42] The explanation has been offered that, if menstrual cycles are indeed in tune with the phases of the moon, the time of the full moon may represent a peak in fertility, thus accounting for a peak in birthrates at about the same time some nine months hence;[41] however, other studies have found no or even a negative correlation between the phases of the moon and birthrates.[43]

The moon has also been tentatively linked to various types of abnormal behavior[44-46] (accounting for the origin of the word "lunacy"), including suicide.[47] Indeed, a number of studies have found that various mental disturbances, particularly depression, exhibit some form of periodicity;[48,49] some such disorders even seem to be *caused* by disrupted or abnormal biological rhythms[50-52] and can be treated by "adjusting" the individual's rhythm through the use of a synchronizer, such as light.[53,54] However, it should be noted that there are difficulties inherent in trying to separate the effects of a possible internal clock on behavior from the external, social cues that occur in a definite rhythm. For instance, an annual rise in the suicide rate is experienced around the Christmas and New Year's holidays in many countries, but this is more likely due to excessive alcohol consumption and cases of depression brought on or exacerbated by the holidays than by disorders akin to SAD.[55]

Remaining Questions

This essay has touched on a number of important areas in chronobiology research, but a few more should be mentioned. One intriguing area of research deals with the effect of biological rhythms on the efficacy of medication. W.J.M. Hrushesky, Department of Medicine and Laboratory of Medicine and Pathology, University of Minnesota Medical School, and Masonic Cancer Center, Minneapolis, notes that in 31 patients with advanced ovarian cancer, the toxic side effects of anticancer drugs (which kill cancerous cells but can also kill or severely in-

jure normal ones) were far more pronounced when the drugs were administered at certain times of the day.[56] Administration time also affects the efficacy of drugs given to alleviate the symptoms of asthma[57] and of indomethacin, an anti-inflammatory agent.[58]

Another important area of research involves biological rhythms and the effects of working late at night or on a continually shifting schedule, briefly mentioned earlier. In a letter to the editors of *Nature*, Simon Folkard, MRC Perceptual and Cognitive Performance Unit, University of Sussex, UK, and colleagues reported a circadian rhythm in the cycle of drowsiness and alertness that was independent of the sleep/wake cycle.[59] This implies that there are certain times of day when workers will inherently tend to be more alert or more drowsy, depending upon their own internal rhythms. And indeed, Robin Dodge, Aerospace Medicine, Wright State University, Dayton, Ohio, notes that definite rhythmic variations in alertness that are independent of lack of sleep have been observed in the crews of airliners.[60]

Chronobiologists are not yet certain what basic mechanisms underlie biological rhythms, nor is it understood how the clocks are set or whether they can be controlled, or reset, outside the narrow range that has been found in experiments so far. However, as we have seen, some intriguing hints concerning the answers to these areas have already appeared.

* * * * *

My thanks to Stephen A. Bonaduce and C.J. Fiscus for their help in the preparation of this essay.

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