BOOKS: PHYSIOLOGY

Tales of Organic Timekeeping

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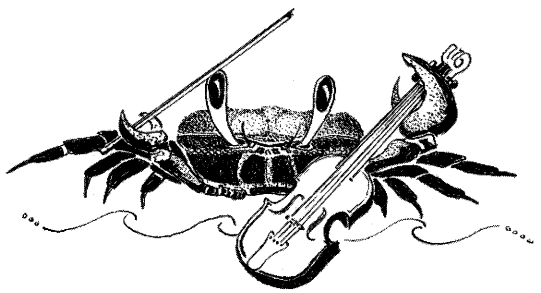
The Living Clock
The Orchestrator of Biological Rhythms
by John D. Palmer
Oxford University Press, New York, 2002. 176 pp. $26, £19.99. ISBN 0-19-514340-X.

A few weeks ago I flew back to the United Kingdom from a conference on biological rhythms in Los Angeles. I've never been one for taking drugs unnecessarily (except maybe in the 1960s), but I was tempted to try one: melatonin, the natural hormone that provides our body with its internal representation of nighttime. The reasons for considering this possibility were several: It might help me sleep better on my return, as my brain would be eight hours out of phase with my body after the overnight transcontinental flight. (This is actually a pretty poor excuse, because I hardly suffer from jet lag at all.) Unlike in the UK, I could just pop down to the local drug store in Westwood and pick up a bottle of pills for about $12. And, as a circadian rhythm geneticist, I was curious to test on myself the effects of melatonin given that my clock colleagues swear by the stuff. So off I went and bought some tablets. The label said "take one an hour before retiring," and I dutifully swallowed one my first evening home in Leicester and waited for the magic to begin and my lights to go out. The next four nights were probably the worst I have spent in my entire life. I tossed and turned, simply couldn't get sleepy, and just lay there until the early morning, when I could feel my body temperature beginning to rise. When I finally dozed off, the alarm soon rudely heralded the impending workday—which, given my exhaustion, was pretty grim. This pattern was repeated for the next three nights, even though I had not taken any more of the damn stuff.

So what went wrong? Well, that's difficult to say. But on reading John Palmer's *The Living Clock*, his chapter on jet lag seems to hold the answer. Apparently (and I missed this research when it first came out), the largest controlled study aimed at examining whether melatonin alleviates the effects of jet lag came up negative (*1*). So maybe my adverse reaction was due to my anxiety at waiting for something to happen (which didn't), compounded by my increasing overtiredness on subsequent days. Needless to say, I got rid of the tablets. If nothing else, Palmer's book has already provided some added value, at least for me.

I have to confess that when I first saw the book, I was not impressed. The cover is nice, but the print is small and dense, there are no color pictures, and as a result the volume looks "old-fashioned." The abstract that had been sent to me earlier was not promising, and I was concerned whether it was accurate.

In the field of biological rhythms, the most exciting work is being done in the molecular arena. So captivated are we by the approach that hardly a month passes when one or more relevant papers do not appear in *Science*, *Nature*, *Cell*, or *Neuron*. And why not? We can all relate to our own daily body rhythm, and half of us, to our monthly cycle. There is something intrinsically fascinating about these oscillations. They are mysterious, yet—as the molecular analysis has shown for the circadian variety—they are beginning to divulge their secrets.



Crabs keeping time. In fiddler crabs subjected to constant laboratory conditions, the tidal activity rhythm and the daily color-change rhythm persist for days to weeks.

The fruitfly *Drosophila* began leading the way in this voyage of discovery when Ronald Konopka, a graduate student under Seymour Benzer at Caltech, published the first mutational analysis of a circadian clock (*2*). The *period* (*per*) mutants, whose circadian clocks ran hours fast or slow, or did not run at all, became the flagships of the new neurogenetic approach to complex behavior. These variants were the platform for the 1984 cloning of the *per* gene and, a few years later, the discovery that the *per* gene products cycled in abundance. In a relentlessly cycling molecular feedback loop, a phase delay between the *per* transcript and PER protein cycles allows the protein to inhibit its own transcription (*3*). The fundamental story has since been embellished with new characters that constitute the core oscillator, including *timeless*, *clock*, *cycle*, *doubletime*, and *shaggy* (*3*). Interest in the molecular biology of biological rhythms increased in the late 1990s when the mammalian clock was found to depend on the same molecules: *period*, *clock*, *cycle*, *doubletime*—all the usual suspects (*4*). Parallel approaches to teasing apart the control of rhythms in the yeast *Neurospora* and later *Cyanobacteria* (yes, even bacteria) and the mustard-like weed *Arabidopsis* led to the discovery of new sets of clock molecules (*5*).

The molecular stories are all jolly exciting, and *Science* has chosen clock research among its annual top-ten scientific stories on a couple of occasions over the past few years. So it is somewhat surprising to find that only about 3 of the 145 pages of text in Palmer's book are devoted to all these modern developments. Is this good or bad? Despite the reservations prompted by my first impressions, it turns out to be good. This is because we have overdosed on reviews about the molecular oscillations that underlie circadian behavior. Palmer, an emeritus professor of biology at the University of Massachussets, Amherst, has previously written a monograph on rhythms of shore-dwelling animals (*6*). Instead of focusing on the hottest new findings, his current book is more a natural history of various types of biological cycles. He writes about all sorts of rhythms—circadian 24-hour cycles, tidal rhythms, lunar cycles, annual oscillations—with a wit and élan that is always engaging, sometimes rather risqué, and often hilarious. For example, there is the round-the-world trip of the senior George Bush, during which he ignored his own jet lag and ended up barfing on the Japanese prime minister's foot. The wonderful creatures that Palmer uses to illustrate his points about biological timing are themselves amazing. Take the marine Palolo worm, from near-shore reefs in Samoa, whose tail end fills with eggs or sperm. At a particular time of year, the animal jettisons it. Off it wriggles with all the other derrieres, until they all literally explode in an orgasm of gamete release and fertilization. The ocean moved, literally.

The Living Clock is not a text for students; a text on clocks is long overdue. Rather Palmer has written a whimsical, "gosh can you believe that" account for

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the interested lay reader, which is also a book that will further fascinate serious chronobiologists with the wonders of their subject. It is a reminder of the marvels of nature and of the critical role that endogenous biological timing plays in the life cycle of almost every organism.

References

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BOOKS: HUMAN GENETICS

Moving and Mixing

Linda Vigilant

Among the first questions one asks a new acquaintance is "Where are you from?" This is not always as simple a question as it may seem. Living in Europe, I have tried to answer with just "the U.S.," but this satisfies nearly no one. "But where in America?" The follow-up gives me pause. Is it New Jersey, where I spent my childhood? California or Pennsylvania, the places I lived as an adult? Which would I rather be linked with: Bruce Springsteen, the entertainment industry, or Three Mile Island? For we tend to use information about a person's place of origin as a shortcut to knowing a whole range of things about them: likely educational background, religion, economic status, political views, and so on. Although I can edit my personal history at will, none of us can choose our ancestors.

The current boom in genealogical research suggests that I am in the minority in finding the history of long-dead ancestors irrelevant. The posting of information on the Internet allows one to ferret out of the names and birth dates of forebears without visits to obscure church registries, and if that information seems a bit dry, genetic analysis can help flesh out the story. There exist labs that are willing, for a fee, to analyze DNA from scraped-off cheek cells, report on the more or less likely geographic origin of the ancestral bearer of a miniscule fragment of the donor's genome, and even provide a matching ancestral legend. Such entrepreneurial geneticists will hope that few read Steve Olson's *Mapping Human History* and discover the truth that, due to the exponential growth in the number of our ancestors, we all are justified in claiming ancestry from say, Julius Caesar, Confucius, or (my personal favorite) Cleopatra.

Why, in an era of increasing mobility and mixture of individuals across traditional class and racial boundaries, are people increasingly fascinated with geographic (read: ethnic) origins? This is a conundrum raised by the book, yet ultimately outside its scope. In all respects, however, Olson does an admirable job of presenting an up-to-date, consensus view of what genetics tells us about who we are and how we got here as a species. The book's central message concerns genetics and race: The classification of humans into racial categories ignores the biological reality of the overwhelming genetic similarity of outwardly different-seeming individuals. Somewhat breathless claims by the dust-jacket commentators notwithstanding, this is not a novel insight derived from the sequence of the human genome. Nonetheless, the author's lucid explication of this theme is noteworthy and valuable, particularly for a general audience. Even some geneticists in the field would benefit from being reminded of the fundamentally misleading nature of population trees, which presuppose a sorting of individuals into neat categories. That populations are composed of individuals who move about is exactly what has made untangling the patterns of human dispersal challenging and interesting.

Mapping Human History
Discovering the Past Through Our Genes
by Steve Olson
Houghton Mifflin, Boston, MA, 2002. 302 pp. $25. ISBN 0-618-09157-2.

Olson duly presents the story of the origin of modern humans in Africa, with subsequent dispersal to the rest of the world. In a particularly effective approach, he then presents a series of chapters that focus on other geographic regions and the particular histories of populations found in each. Other books cover similar ground, but a notable advantage of *Mapping Human History* is the author's background. He is a science writer with a broad knowledge of the literature, rather than a researcher who might have a vested interest in presenting a particular interpretation or even be tempted to engage in a bit of image-polishing.

Researchers' voices are not absent, however, and comments from both major and less-prominent geneticists enliven the presentation. Many express the hope that, among other things, the results of their work will serve to allay racial prejudices. Unfortunately, scientists can also be astonishingly unaware of potential negative implications and misconstructions of their work. This is all too apparent in the debacle of the Human Genome Diversity Project: The seemingly well-intentioned goal of cataloging worldwide variation in humans through a comprehensive genetic survey instead elicited distrust and hostility from the "native" peoples of interest. It remains to be seen how ably researchers interested in studying disease-associated genetic polymorphisms in particular groups of humans will manage similar challenges. Furthermore, while few would contest the justice of returning the remains of contemporary victims of scientific racism for burial in their native lands, other sets of remains—such as the case of the 9500-year-old Kennewick Man found in North America—pose a difficulty. Because we are all connected genetically a few thousand years back, who is entitled to claim ownership of a set of bones, or some artifacts, or a piece of land?

Looking toward the future, Olson is inspired by a visit to Hawaii to imagine "a world in which people are free to choose their ethnicity regardless of their ancestry." Thus, in practical terms race will become divorced from genetics, in people's minds as well as in biological reality. One could argue that it is clear that race has already become less meaningful today, to judge by the depressing extent of recent and ongoing armed conflict between physically indistinguishable groups. To whatever degree it may help, *Mapping Human History* lucidly conveys the utter senselessness of categorizing people in the face of the interconnectedness of all humanity.

A sample of human diversity in Hawaii.

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