

# Michael Rosbash

## *A biological clock*

**T**ime: why and how do living organisms harmonize with the fourth dimension of our world?

Many biologists have little interest in this question. They concentrate instead on the three-dimensional world, trying to understand how the proper size and shape of organisms are encoded and achieved, and how the human brain is wired. Although these matters are not completely divorced from temporal considerations – an organism must make the correct gene products in the correct sequence and at the correct stage of development – timing has received scant attention during the past thirty years or so in such fields as molecular and developmental biology.

In contrast, other biologists, working in such fields as neuroscience and evolutionary biology, regard the issue of time as urgent and inescapable. Consider the

brain. There are very rapid temporal events, of intense interest to neurobiologists, on the millisecond (0.001 seconds) timescale. Here timing is everything, and information-processing in a neurobiological context does not work at all if events do not occur with proper speed and coordination.

Then consider the evolution of life on earth. It has taken three to four billion years for our species to emerge since primitive life-forms first arose in the primordial soup. The last 0.1 percent of this journey, approximately five million years, is the time since the last common ancestor shared between humans and our closest relatives, chimpanzees. It is generally acknowledged that many features unique to our species, like walking upright and sophisticated verbal communication, arose during this last tiny fraction of our planet's biological experiment. Yet even this 0.1 percent, or 5 million years, is a number that dwarfs the average human life span and comprises perhaps two hundred fifty thousand to five hundred thousand ape-human generations.

The incredibly slow march of evolutionary time and the very rapid events of neuronal firing are well beyond the experience or intuition of most if not all members of our species. The inability of people to achieve a comfortable relation-

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ship with these very large and very small numbers has almost certainly contributed to society's difficulties with mind-brain issues on the one hand and Darwinian evolution on the other.

No such difficulties attend the topic of my own area of biological interest: the circadian rhythms that regulate living organisms. These rhythms function on the much more familiar timescale of twenty-four hours. The name 'circadian' comes from the Latin *circa dia* and means 'about a day.' This is because circadian periods do not last *exactly* twenty-four hours but rather vary somewhat from organism to organism. These inexorable rhythms, due to the persistent beating of a biological clock in our brains and in other tissues, serve to coordinate many features of our behavior, metabolism, and physiology – even our sleep-wake cycle. Circadian rhythms are also present in plants and in most, perhaps all eukaryotic life-forms, i.e., complex organisms like us with a nuclear membrane. Bona fide circadian rhythms are even present in some photosynthetic bacterial species.

The relationship to photosynthesis is not coincidental, as circadian rhythms reflect an almost ubiquitous adaptation to the twenty-four-hour-day cycle. The rotation of the earth on its axis is the source of daily temperature as well as of light-dark cycles and is considered the oldest and most continuous feature of life on earth. Even the first organisms – perhaps the self-replicating molecules of the original RNA world that probably preceded cellular life – arose in the presence of a light-dark cycle much like the one we experience today. It was perhaps 20 percent shorter four billion years ago, which might contribute to the explanation of why circadian clocks are not precise twenty-four-hour timekeepers. Con-

sistent with the loose relationship to a twenty-four-hour cycle, intrinsic period varies from species to species, from about twenty-two to about twenty-six hours.

The fact that there is a difference between the 'intrinsic period' of an organism and the actual twenty-four-hour cycle of the external world implies that circadian clocks are not solely light-driven. From a practical standpoint, it also implies that the intrinsic period must be measured under constant conditions, constant darkness or constant light along with constant temperature. This is to avoid the synchronization with the actual twenty-four-hour light-dark cycle that normally takes place.

It is generally acknowledged that the first person to recognize this organic phenomenon was an eighteenth-century French astronomer named de Mairan. He had been musing about plant rhythms, wondering what drove plants to extend their leaves during the daytime and retract them at night. Intuition suggests that this daily leaf movement rhythm should be light-driven, but in 1729 de Mairan elected to test this hypothesis. To perform the first free-running circadian experiment, he took a plant down to his basement (*la cave*), where there were constant conditions, i.e., no daily variations in light or temperature (good for storing wine). *Mirabile dictu*, the leaf movements continued unabated on a circa twenty-four-hour schedule, indicating that they were driven by an endogenous circadian clock rather than by light.

Many different kinds of experiments under constant conditions support this general conclusion, namely, that most organisms contain self-sustaining pacemakers at the heart of their circadian systems. Mice have periods of about 23.5 hours and rats about 24.5 hours under

constant conditions. Importantly, there are even differences between inbred strains of mice, indicating that quantitative features of the circadian system are under genetic control. (Much more about genetics and mutants below).

Under more normal light-dark conditions, animals sense light and especially the changes in illumination intensity that are normally experienced at dawn and dusk. Photoreceptors transmit these time-of-day signals through specific input pathways to their endogenous biological clocks. One or more of these photoreceptors provides a daily reset of these endogenous clocks and keeps them synchronized with the actual twenty-four-hour light-dark cycle of the external world. A one-hour delay remains a one-hour delay, day after day, and every day is the same as the day before. Otherwise put, circadian clocks run too fast or too slow, but they are reset at the same time every day by the very precise twenty-four-hour light-dark cycle. This general principle gives rise to an important relationship between period as measured in constant darkness and phase as measured under more normal light-dark conditions. An individual with a shorter period under constant conditions will usually manifest an advanced phase under normal conditions. This pertains to comparisons between species as well as between individuals of a single species – a mutant for example.

What are circadian mutants and how do they arise? It is important to appreciate that mutants in general (mutants of any characteristic and of any organism) are of two kinds. First, there are spontaneous mutants, oddballs that arise by chance. These are oddballs in the probability and statistics sense of the word, with no pejorative connotation implied. They might have one or more unusual circadian characteristics, which are

genetic in origin, due for example to a fortuitous mutation in an important clock gene. (This is fortuitous for the investigator; not always for the individual, if we are considering humans.)

The second, larger category of mutants is induced. This is usually due to the feeding of mutagens to animals or bacteria, which causes a high frequency of DNA alterations and a concomitant high frequency of mutations. (Needless to say, this is not done with humans.) The strategy is then to screen the treated population for a mutant phenotype, a circadian abnormality for example, and verify that it 'breeds true' and is transmissible to subsequent generations. This 'forward genetics' approach (called 'genetics' before the more recent advent of recombinant DNA and 'reverse genetics') has been a mainstay of biological research for much of the twentieth century, both in microorganisms as well as more complex organisms like *Drosophila* (fruit flies). This canonical strategy was originally concerned almost exclusively with mechanisms of inheritance, i.e., how particular characteristics (phenotypes) are transmitted from generation to generation. This more descriptive field of genetics predominated during the first half of the twentieth century and presaged the Watson-Crick discovery of the structure of DNA in 1952 – 1953.

A more biochemical genetics, the study of gene expression, has predominated since that time. Especially over the past thirty years, this has given rise to an abundance of information about genes and their functions. The recent completion of the human genome DNA sequence, approximately three billion base pairs per person, is a particularly visible example of this progress. The worldwide effort to understand DNA and its expression has provided the world of molecular biology with a highly sophisticated

tool kit, culminating in the now rather straightforward ability to identify and sequence a mutant gene and identify the precise genetic lesion – the genotype responsible for the appearance or relevant characteristic(s) of the mutant organism – the phenotype.

It was against this general backdrop that Seymour Benzer decided in 1965 to apply genetic strategies in an effort to explain enigmatic behavioral problems like circadian rhythms and memory. Benzer had made a large contribution to the understanding of gene expression during the 1950s and early 1960s, and he had a fascination with behavior. Although studied for a long time in many organisms including insects, these problems like circadian rhythms and memory were almost intractable from a molecular standpoint. This is despite the fact that electrophysiologists and pharmacologists had been working successfully on the mechanisms that underlie the basic structure and function of neurons. There was still no obvious way to gain access to the genes and especially to the proteins that must constitute at least part of the biochemical machinery that lies at the heart of rhythms and memory. (Proteins are involved in just about everything biological.)

The genetics and molecular biology community was brimming with confidence after its remarkable success at providing mechanistic explanations for inheritance and the genetic code. As a consequence perhaps, Benzer and others found unsatisfying the descriptive (non-biochemical) approaches and explanations used in behavioral studies. With almost religious zeal, they believed that genetics was the path to enlightenment. This new approach to behavior also represented a paradigm shift for the field, as it went from being an end in itself to being a means to very different ends.

Understanding the 'mechanism of inheritance' was no longer the goal. Rather, the goal became understanding the biochemical underpinnings of behavioral biology. The research strategy was simple: isolating a mutant gene associated with aberrant circadian rhythms will identify the underlying biochemical cause of the behavior. For example, a mutant clock gene will encode a mutant clock protein (genes → RNA → protein; the central dogma of molecular biology), which can be mapped by traditional procedures and then used to further probe clock mechanisms.

The genetic approach that Benzer pioneered is not without controversy. Does the existence of clock genes (or memory genes, or sex-drive genes) mean that human behavior is hardwired by our genes, with no room for environmental influence? If we have behavioral genes, what room is there for free will and responsibility? Few people question the inheritance of height, hair color, or eye color from parents to children. Almost everyone seems to agree that tall parents are more likely to have tall children. (The genetics can be complicated, so the outcomes are statistical within a population, i.e., it doesn't always work in every case.) But the possible inheritance of brain characteristics (personality, sense of humor, and intelligence for example) raises hackles for almost religious reasons: the brain appears to be divine territory. On this issue, many neuroscientists stand firm and believe that all behavioral phenomena ultimately will have biochemical underpinnings. This does not negate the fact that the underlying mechanisms in many cases (e.g., complex reasoning, consciousness) may be very complicated and beyond our grasp for years and perhaps even decades.

It is important to understand that the possible inheritance of behavioral properties from parents to offspring in hu-

he 'mechanism of inheritance' is no longer the goal. Rather, understanding the genetic underpinnings of behavior research strategy was to identify a mutant gene associated with circadian rhythms will be revealing biochemical information. For example, a mutant gene will encode a mutant protein; DNA → RNA → protein; (the language of molecular biology), developed by traditional procedures to further probe the mechanism.

It is a truism that Benzer pioneered the field of circadian rhythm out controversy. Does the clock genes (or memory genes) mean that hardwired by our genes, environmental influences on behavioral genes, what free will and responsibility? The question is the inheritance of hair color, or eye color in children. Almost everyone knows that tall parents are likely to have tall children. (The inheritance is complicated, so the outcome is not always within a population, but it doesn't always work in every generation.) The inheritance of intelligence (personality, sense of humor, etc.) almost always seems to be divine intervention. Many neuroscientists would believe that all behaviors are ultimately determined by genes. This does not mean that the underlying mechanisms in many cases (e.g., consciousness) may be beyond our grasp and beyond our grasp perhaps even decades ago. It is to understand that the nature of behavioral properties is passed to offspring in hu-

mans has little to do with the genetic strategies in model organisms designed to illuminate brain-behavior mechanisms. Researchers interested in human genetics – i.e., the possible inheritance of behavioral properties from parents – focus on the question: Are brain phenotypes that distinguish different human beings heritable? The question Benzer posed was: Can I identify behavioral genes in a model organism, and will they illuminate something fundamental (and hopefully ubiquitous) about the underlying mechanisms, even in humans? Attempts to answer the human genetics question rely on an uncertain principle and subtle analyses of phenotypic differences between individuals.

The model organism genetic strategy, by contrast, uses an experimental sledgehammer to debilitate a key gene and hopefully create a striking phenotype, in every offspring from that original mutant. If the phenotype is robust and maps to a single gene, it should provide an entrée into what might otherwise be an intractable scientific problem. This strategy has proved to be a staggering success for biological clocks and learning and memory, and we now have a fairly sophisticated grasp of the relevant biochemical machineries.

Benzer and his student Ron Konopka first explored the genetics of circadian rhythms by studying fruit flies. Their research, published in 1971, resulted in the identification of the first clock gene. By mutagenizing and screening progeny for their locomotor activity rhythms (rhythms of rest-activity cycles, more or less the insect analog of our sleep-wake cycle) in constant darkness, they identified three types of circadian-rhythm mutants: a short-period mutant (nineteen-hour period), a long-period mutant (twenty-nine-hour period), and an arrhythmic mutant with no rhythms what-

soever. All three mutants were allelic, i.e., they were all due to mutations in the same gene, which they named *period*.

This was not only a landmark achievement, which kick-started the circadian rhythm field, but also unusually prescient. This first clock gene was identified several years before the first recombinant DNA papers appeared in the scientific literature, and a decade or more before the cloning of genes became a truly practical technology, even in sophisticated laboratories. In other words, the period mutants were identified and characterized by Konopka and Benzer well before the more complete molecular genetic vision was conceptualized, let alone realized. Although these mutants gave Konopka and Benzer as well as others an invaluable tool with which to manipulate the circadian system of flies, another thirteen years passed before the period gene was cloned and identified by molecular methods.

In the intervening years, Konopka continued to work on *Drosophila* clocks with traditional tools, as a faculty member at Caltech and then at Clarkson College. At the same time, I was doing molecular biology on completely unrelated subjects, first as a postdoctoral fellow in Scotland, and since 1974 as a faculty member at Brandeis University. I did not read or even hear about the Konopka and Benzer paper until the mid to late 1970s, from my friend, colleague, and ultimately long-term collaborator Jeff Hall. He was a contemporary of Ron Konopka in the laboratory of Seymour Benzer and continued to work on behavioral genetics and fly courtship after he took a faculty position at Brandeis, also in 1974. (Hall and Konopka remain friends to this day.)

Hall was also doing some work on circadian rhythms, because the period mutants had a pronounced effect on a particular aspect of fruit-fly courtship. In

1982, after the recombinant DNA revolution had transformed my laboratory as well as many others, Jeff Hall and I decided to apply these new technologies to the problem of circadian rhythms and clone the period gene. At that time, he was the *Drosophila* rhythm guru and I the molecular biologist, and we published our successful results in 1984. Importantly, the gene was identified by germ-line transformation, in which the phenotype of the mutant flies was altered by injecting cloned wild-type DNA. ('Wild type' is genetic patois for a normal, as opposed to mutant, individual or gene.) The phenotype was converted back to that characteristic of a wild-type strain, showing that the injected DNA contained the normal gene. Mike Young at Rockefeller University used a very similar strategy and published the same result at essentially the same time. This was the first transgenic rescue of a behavioral gene in any organism.

Unfortunately, this achievement was still not entirely satisfying. This is because a key aspect of the circadian system, the period protein (PER) and particularly its function, remained unknown. Both our laboratories at Brandeis and the Young laboratory at Rockefeller worked on the relationship of this gene to circadian rhythms during the next few years, which resulted in several significant advances. We both mapped the sequence of the complete protein and located the precise nucleotide changes responsible for the slow, fast, and arrhythmic alleles. However, knowing the DNA sequence still did not explain the function of the period protein. This is because it was a 'pioneer protein,' with no known relatives. In those early days of DNA sequencing, with only limited database information from different organisms, it was much more the rule than the exception that a DNA sequence

did not reveal the function of a protein. (Although less problematic today, the function of perhaps 50 percent of human proteins is still uncertain.) This was the situation until 1988, when there appeared the sequence of a well-understood *Drosophila* protein with a clear relationship to the period protein. This relative was a known transcription factor, meaning that it functioned in gene expression to 'transcribe' DNA into RNA. Although the two proteins were not very close relatives and only a limited portion of the protein sequences was in common (and the region in common was itself of uncertain function), the similarity was unambiguous and inspired us at Brandeis to explore the following hypothesis: Perhaps PER itself was a transcription factor – and if it was, then perhaps the regulation of transcription was central to circadian rhythms.

In 1990, almost twenty years after the landmark Konopka and Benzer publication, we published the finding that period messenger RNA (mRNA) levels undergo circadian oscillations and that PER regulates the period and phase of its own mRNA cycling. In other words, the mRNA cycling was sensitive to the Konopka and Benzer mutations and paralleled the previously described changes in the behavioral cycle. (Remember: DNA → mRNA → protein; synthesis of mRNA using DNA as a template = transcription and synthesis of protein using mRNA as a template = translation.) Over the next several years, we expanded on this observation and showed that the fluctuations in period mRNA levels were largely transcriptional and almost certainly reflected a negative feedback loop, in which PER inhibits its own synthesis.

Then, in 1997, the field experienced another major breakthrough: the discovery of the mammalian period genes. For the first time, it became clear that

unction of a protein. (Schematic today, the 50 percent of human certain.) This was the , when there ap- e of a well-under- otein with a clear re- riod protein. This re- transcription factor, ctioned in gene ex- ibe' DNA into RNA. roteins were not very only a limited portion ences was in common ommon was itself of ), the similarity was nspired us at Bran- following hypothesis: was a transcription s, then perhaps the ription was central is.

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the same transcriptional feedback loop occurred in mammals – including human beings – and not just in fruit flies. This important finding unified the worlds of mammalian and insect rhythms and indicated that a very similar circadian machine operates in all complex animals. Indeed, almost all of the additional fruit-fly pacemaker components discovered in the past decade are conserved across species. These include proteins that contribute to important circadian posttranscriptional control mechanisms. (For the cognoscenti, this includes RNA and protein stability as well as protein phosphorylation.) The conservation of functional clock components echoes a major biological theme from DNA work in many fields over the previous two decades, namely, the same genes make the same proteins and do the same basic jobs in all complex animals.

In other words, circadian rhythms are ancient. These biological clocks existed many hundreds of millions of years ago – long before the evolution of insects and mammals.

Although there is a similar clockwork (the circadian quartz crystal) in all animals, the machinery ticking in plants and fungi appears quite different – from each other as well as from that in animals. Although there is a very limited relationship between a couple of animal clock genes and those in *Neurospora* (a type of bread mold and an important circadian clock model organism because of its genetics), it has long been generally believed that circadian rhythm genes are not truly shared among all three kingdoms: animals, plants, and fungi. A commonly articulated conclusion is therefore that circadian rhythms arose multiple times in evolution: animal clocks come from one beginning, and

the clocks of plants and fungi from another (or from more than one). The situation contrasts with the protein synthesis machines of plants, animals, and even bacteria. They are so similar that it is universally accepted that protein synthesis arose only once in evolution and has been passed on to all contemporary organisms from a single common ancestor.

This multiple clocks hypothesis has to deal with the fact that the molecular design principles of these different clock systems are quite similar, i.e., they all involve the circadian regulation of different transcription factors. This points to convergent evolution subsequent to multiple origins as the explanation for the similar design plans.

But in my view, a still more attractive possibility is that key common elements – missing links between the systems – are as yet undiscovered, or insufficiently appreciated. Two recent studies have shown that the protein kinase CKII (casein kinase II; a kinase puts phosphate groups on other molecules) is a clock gene in *Drosophila*. As this enzyme had been previously implicated in the clocks of plants and *Neurospora*, it is the first clock component shared between all three systems and may reflect a common evolutionary origin for the circadian system in eukaryotes.

Because CKII plays a pivotal role in the response to ultraviolet radiation in organisms ranging from yeast to humans, it is possible that avoiding UV light was a major driving force in the early evolution of circadian systems. This idea is also based on other considerations, centered on light and its important relationship to circadian rhythms. Although sunlight is a primary source of energy for life on earth (via photosynthesis) and is important for vision, it also provides a critical temporal cue for circadian sys-

tems. Indeed, most organisms have evolved specialized photoreceptors for circadian light perception. In *Drosophila* and insects, the protein cryptochrome serves as a major circadian photoreceptor, whereas rhodopsins are the major visual photoreceptors (this is the same family of proteins that is used for visual photoreception in mammals, including humans).

Although mammalian cryptochromes may also be circadian photoreceptors, the evidence is stronger that they are important central clock components. Importantly, cryptochromes are close relatives of photolyases, which are blue light-activated DNA repair enzymes. This connection leads to the idea that the strong UV component of sunlight contributed to the selective pressure for the evolution of this specialized photoreceptor. Moreover, the blue light absorption maximum suggests that circadian photoreception may have evolved in an aquatic environment shortly after animal life first emerged, because only blue light can penetrate to substantial depths in water. This is related to the suggestion that diurnal fluctuations of some animals in the oceans (deeper in the daytime, more shallow at night) are to avoid UV irradiation. Early photolyases may then have signaled both the time to descend and especially the time to rise to the surface, a precursor of the circadian rhythm role played by their contemporary descendents, cryptochromes.

*Drosophila* cryptochromes function as photoreceptors within most if not all individual clock cells. This is related to the fact that the self-sustaining transcription-translation feedback loop that lies at the heart of the circadian system is cell-autonomous, i.e., it operates independently within the many circadian cells and tissues. A major factor keeping these individual clocks synchronized is their independent connection to the

light-dark cycle, through the cell-autonomous function of this photoreceptor. Even within the fruit-fly brain, cryptochromes receive direct time-of-day information from sunlight and transmit it intracellularly to the clock machinery. They are therefore true deep-brain photoreceptors that bypass the eyes as a pathway for photic information.

In contrast, many mammals, including humans, have an opaque skull and must therefore use their eyes as the source of temporal as well as visual cues for the brain. Yet even in mammals it is virtually certain that separate molecules and even separate cells of the eye are used for circadian and visual photoreception. This is because the rods and cones, which house visual photoreceptors, are unnecessary for circadian photoreception. Only very recently have specific retinal ganglion cells, putative circadian photoreceptor cells within the retina, been identified. They contain a specialized photoreceptor (melanopsin), which transmits information to the circadian pacemaker region of the brain. This is a small part of the hypothalamus called the suprachiasmatic nucleus (SCN). It is the most important region of the mammalian brain for orchestrating the circadian programs of the entire organism. SCN cells contain a robust transcription-translation cycle, which relies on the eye for its photic information.

The importance of the retina to mammalian circadian rhythms has profound implications for many blind people. These individuals 'free-run' with an endogenous period characteristic of our species, slightly longer than twenty-four hours. As a consequence, they periodically move out of sync with the rest of the population and then have a myriad of physiological and behavioral difficulties. This is because they cannot perceive the actual twenty-four-hour light-dark



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cycle that keeps most of us regular and 'on time.' The affected population is difficult to identify with vision tests, because of the photoreceptor division of labor mentioned above. Individuals with an intact melanopsin system are presumably able to 'see' circadian cues, independently of other visual difficulties. The blind population not only also underscores the importance of the eyes for the circadian system, but also indicates that other potential cues (temperature, noise, social interactions) do not have much influence on human circadian timing.

The circadian system also influences the human sleep-wake cycle. When circadian-blind individuals are out of sync with the twenty-four-hour light-dark cycle, they have trouble falling asleep at night and rising at a normal hour for work or school; for obvious reasons, they then experience excessive daytime sleepiness. These difficulties resemble some sleep disorders, which have long been interpreted as being circadian in origin. These include Advance Sleep Phase Syndrome (ASPS) and Delayed Sleep Phase Syndrome (DSPS).

Individuals with these disorders have a normal sleep drive, which just kicks in too early or too late compared to most of us and creates obvious conflicts with most of the human population. ASPS individuals become sleepy and fall asleep in the early evening, at perhaps 7 P.M. They then sleep a normal and restful seven to eight hours and rise at 2-3 A.M. DSPS individuals have trouble falling asleep until perhaps 4 A.M. and then want to sleep a normal eight hours until noon. ASPS individuals are therefore phase-advanced with respect to the light-dark cycle, and DSPS individuals phase-delayed.

Both groups are believed to have defective pacemakers, which run too fast or too slow. With normal ocular connec-

tions, however, they are reset every day by the normal light-dark cues and therefore maintain a constant but aberrant phase relationship with the external twenty-four-hour cycle and the rest of the circadian world. In some cases, this interpretation has been verified in a sleep lab, where the influence of the external light-dark cycle can be removed and the intrinsic period measured. This patient population therefore illustrates the important relationship between phase in a light-dark cycle and intrinsic period in constant conditions mentioned above. Fast or slow clocks have short or long periods, but these are normally masked by the daily reset from the external twenty-four-hour light-dark cycle.

It is interesting to note that the mutant fruit flies studied by Konopka and Benz-er were similarly able to adjust their behavior. Although two of the circadian mutant strains were originally identified as period-altered in constant darkness, the mutant clocks nevertheless manifest perfect twenty-four-hour periodicity when exposed to a normal light-dark cycle. However, like people with ASPS and DSPS, the mutant fruit flies have phase-advanced or phase-delayed locomotor activity patterns under these conditions.

The link between human and fly clocks, as well as between sleep and circadian rhythms, has been further strengthened by the identification and characterization of a family with inherited ASPS. This unusual circumstance allowed researchers to identify the 'mutant' gene responsible for the inheritance of this sleep syndrome. It turned out to be a mutation in a human period gene, the ortholog of the original *Drosophila* clock gene. (An ortholog is a gene that looks the same and does the same job in another, distantly related organism.) The mutation is in one of the three

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human period genes, which perform overlapping and similar clock tasks to the single fruit fly gene.

What lies ahead? From a practical standpoint, we may expect to see new classes of pharmaceuticals, better able to treat disorders of sleep and the problem of jet lag. From the standpoint of basic science, new molecules and principles will almost certainly be discovered. This is because there is a great deal that we still do not understand about circadian clocks and how they function. And only time will tell where modern biology will go in explaining how and why living organisms harmonize with the fourth dimension of our world.

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