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Biological Clocks

by Marc Richelle

SUPPOSE A WHIMSICAL AUTOCRAT banished all timepieces — watches, clocks, sun dials, hourglasses. Most of us would become disorganized; others certainly would undergo intolerable stress. We have come to rely so heavily on man-made timers that it would be almost impossible for us to live without them.

A French speleologist, Michel Siffre, spent several long periods isolated in a cave. He had no time-keeping device. He could talk to the persons who were monitoring his reactions outside the cave, but they could pass no information to him. Siffre was wired for measurement of his physiological responses, including brainwave activity. If he told his monitors that he was going to sleep, they could easily tell when he fell asleep by the change in his electroencephalograph pattern.

In one of his experiments Siffre lived alone underground for 58 days. He had 57 periods of sleep and waking, which is very close to the normal 24-hour cycle (it was on the average 24 hours, 6 minutes). But he thought that he had stayed in the cave 33 days. It was not an error in calculation—he interpreted some of his sleeping periods as after-luncheon naps.

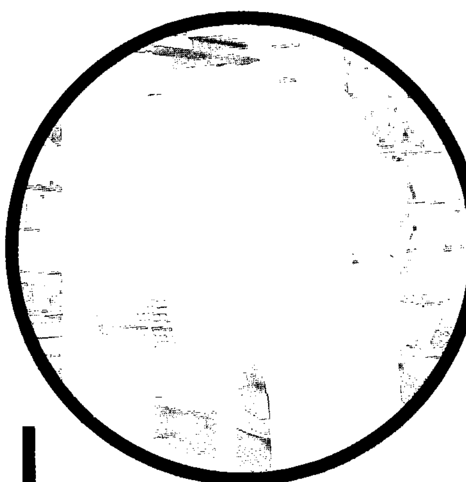
Similar time distortions are reported in accidental cases of complete isolation, such as mine accidents, and in sensory-deprivation-chamber experiments.

Signals. If you feed animals at the same time every day they soon come to the feeding place almost precisely when the food is due. Of course many external signals, such as the position of the sun, might be used by the animals to determine the feeding time. But in a number of cases when all the external signals are eliminated, the animals still come to the feeding place when food is due. It is as if they possess internal time-keeping mechanisms.

Bees show great precision in coming to a place where there is food at exactly the same hour each day. Bees tested in sound-proof chambers, in constant light and in constant darkness remained precisely punctual. By lowering the temperature, one could affect their timing, but could not explain it. Even when they were taken down into a deep salt mine or sent by jet across the Atlantic, bees kept precise time.

Clocks. This rhythmic activity is almost universal in nature, from unicellular algae to man. Biological clocks, as they are called somewhat metaphorically, have become the focus of extensive research in recent years. The phenomenon attracted the attention of scientists more than two centuries ago. Carl von Linné, the Swedish naturalist who in 1750 founded the modern system of botanical nomenclature, proposed to use flowers to build a living clock. Different flowers would open and close at regular intervals to indicate the time of day.

ACTIVITY WHEEL. Records running activity. Rat has free access to drum from cage.



The best known, and perhaps the most important, rhythm of living things is based on a 24-hour cycle. Because it follows the day-and-night alternation, scientists refer to it as the *nychthemeral* rhythm (from the Greek words for night and day). In most animals, sleep-wake periods, body temperature, urination, metabolism rate, heart rate, blood pressure and other physiological functions have typical nychthemeral rhythms.

Drum. Spontaneous general activity in small mammals often is measured with an activity wheel. It is a wire-mesh drum that turns when the animal walks or runs in it. The animal has free access to the drum from its home cage. Each movement or revolution of the wheel can be recorded automatically, and often several months of daily activity are recorded in a single experiment.

Rats are nocturnal animals: given 12 hours of darkness and 12 hours of light, they will do almost all of their drum-running in the dark.

It is apparent that the 24-hour cycle

reflects some kind of adjustment of living organisms to the natural cycle of sunlight. But the remarkable thing is that this rhythm is so deeply rooted in the biological system that it persists—even when all the cues associated with the day-night cycle are eliminated.

One can keep a rat in constant darkness or constant light at a constant temperature, constant noise level, constant everything (even blindness) and the creature will continue to run in the drum at regular intervals. The rhythm, though it is regular, may drift away from the normal 24-hour cycle. The periods of activity may come a little sooner or a little later, but they remain regular. This is why it has come to be called the circadian rhythm (*circa dies* = about a day).

Even complete disruption does not seem to interfere with the working of the biological clock. Curt P. Richter of Johns Hopkins Medical School has shown that when a blinded rat undergoes strong electroshock its motor activity is suppressed for several days. But when it recovers, it resumes activity at exactly the same point in its schedule that it would have been in if nothing had interrupted the daily cycle. It is as if the hands of its biological clock were temporarily stopped but the clockwork continued to run.

Fruit flies. Cues such as light, darkness, temperature, etc., are called synchronizers. With some organisms, when the synchronizers are absent the circadian rhythm fades out. For instance, fruit-fly eggs have a circadian hatching pattern. In constant darkness the rhythm fades and the rate of hatching becomes random. However, switching from constant darkness to constant light will restore the circadian rhythm of hatching. Even a single four-hour exposure to light will reinstate the rhythm to eggs kept in the dark.

These circadian rhythms do not have to be acquired or learned. Fruit flies, mice, rats, chickens and lizards born and raised under constant conditions have regular cycles of activity. The rhythm to some extent is inherited. Even animals that have been raised for several generations under constant conditions continue to show a circadian rhythm.

The rhythm does not require a nervous system or muscular system; it is found in plants and single-cell organisms. It seems to rise from biochemical reactions at the cellular level.

Plural. The circadian cycle is only one of many rhythms, some shorter, some considerably longer. Some are synchronized with others; some apparently act independently. There is no reason to suppose that all of them depend on one internal timing device, and it is more reasonable to talk about internal *clocks* than about the internal *clock*.

In some cases regularity of rhythm is typical of health, and irregularity indicates a pathological condition. An example of this is the menstruation cycle in women, which is disturbed by various physical and psychological ailments. In other cases unusual regularity is associated with disease. Some persons suffer from intermittent hydra-arthrosis in which a knee swells in regular seven- or 10-day cycles.

A forced change in a biological rhythm can lead to physiological and psychological problems. For most normal persons, going onto night-shift work produces a temporary desynchronization of habits and behavior patterns. But while some rhythms adjust to the new conditions, others persist in their former patterns.

Jets. A satisfactory adjustment might never occur if conditions are changed frequently. If you fly from New York to Paris your eating and sleeping patterns will be disrupted. It usually takes 10 to 15 days to adjust to the new cycle. If you fly between New York and Paris every weekend you will continually interfere with your body's attempts to regain a normal rhythm.

This is a serious problem in aeronautical medicine. Jet-plane crews fly through many time zones in a matter of hours. In a recent study of 150 pilots on the France-Pacific route, Philippe Chemin found that more than 70 per cent had extreme difficulty in going to sleep after landing in Papeete. The quality of sleep was altered and the pilots woke up frequently. After 10 to 15 days in the Pacific area they adapted to the local rhythms,

(Continued on page 58.)

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but then experienced similar disturbances when they flew back to Paris.

About 20 per cent of the pilots resorted to hypnotic drugs to help them sleep, while normally only two per cent of the pilots used sleeping pills. Frequent disturbances of the digestive tract also were observed. These are the overt symptoms; underlying them are a number of disruptions in the physiological system. As more and more persons fly vast distances on jets, it is important that the effects of time-zone changes be investigated. It is still an open question whether flying East or flying West produces greater stress on the traveler.

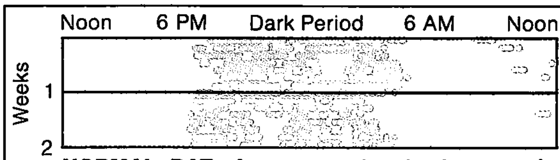
Physicians often prescribe drugs to be taken at an easily remembered time—say at lunch—rather than at 3:10 p.m. But some drugs have different effects at different times of the circadian cycle. If a drug is known to be more effective, or less toxic, at some specific phase of the circadian cycle, physicians could take advantage of this in their prescriptions.

Cats. Internal clocks can be used to adjust to environmental conditions unrelated to the basic natural rhythms. For example, in operant conditioning a cat in a Skinner box can be trained to press a lever for food. If the food reinforcement is given for the first response two minutes after the cat last received food for pressing the lever, the cat will soon develop a typical pattern of waiting until reinforcement time comes up again. Though the cat is free to press the lever during the nonreward period, it does not do so. Rather, it waits until the reinforcement time comes up, then starts pressing the lever, at first slowly, then faster and faster, until it gets food.

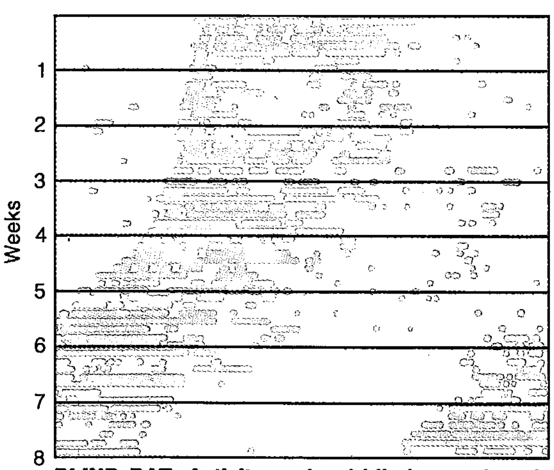
If the waiting time between rewards is changed to five minutes or eight minutes, the length of the pauses in the cat's activity increases so that it covers approximately the same proportion of the waiting time. For instance if a cat waits 75 per cent of the nonreward period before pressing the lever in a two-minute delay between rewards, the same cat will wait 75 per cent of a five-minute delay period or 75 per cent of an eight-minute delay period before pressing the lever.

This acquired regulation is very stable in a well-trained animal, and is fairly constant for each individual animal. The animal is given no external time cues. The temporal regulation it develops is spontaneous and obviously must depend on some internal mechanisms.

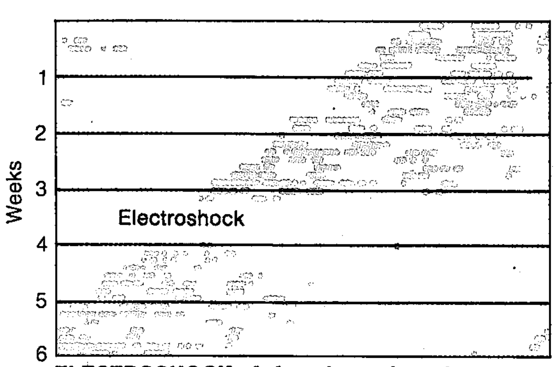
A cat will retain its acquired regulation even if it is not tested for several weeks. We gave a two-month summer vacation to some of our cats and in the first experimental session after that they responded with exactly the same temporal pattern as before. This type of



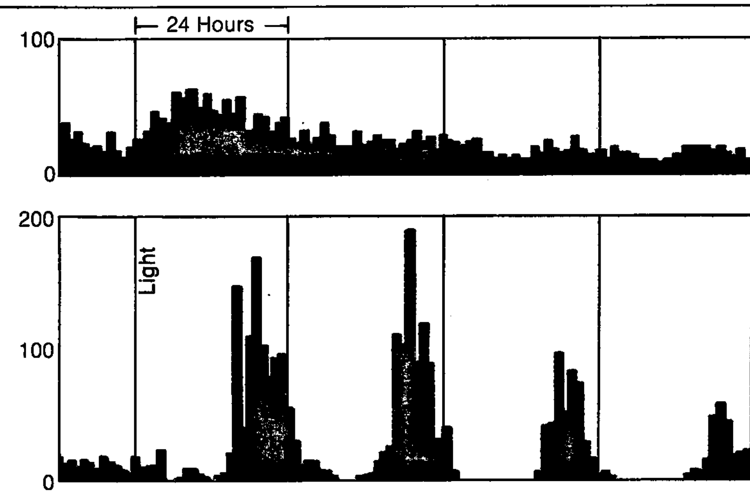
NORMAL RAT. As nocturnal animals, rats do most of their spontaneous running in the dark.



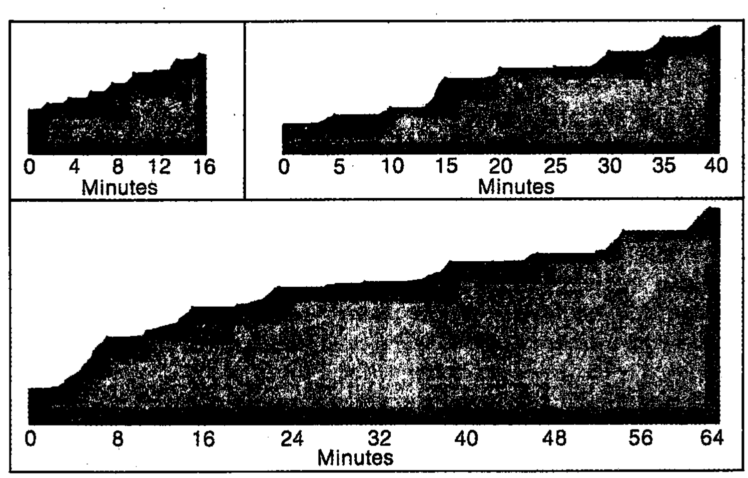
BLIND RAT. Activity cycle of blind rats, though regular, may drift from normal 24-hour period.



ELECTROSHOCK. A few days after electroconvulsive shock, blind rat resumes running exactly according to schedule set by its internal clock.



HATCHING OF FRUIT FLIES. No rhythm is apparent in the hatching rate of *Drosophilae* eggs when they are kept in the dark. A single exposure to four hours of light will reinstate the circadian rhythm.



CAT CLOCKS. Operant-conditioned cats wait until it is time to receive a food reward before pressing a lever. Oblique pips indicate reward. Each upward movement of the curve indicates a press on the lever.

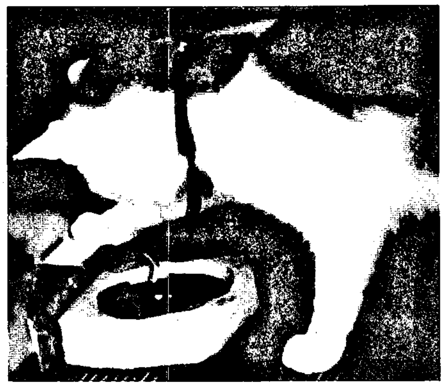
spontaneous regulation is strikingly similar to that described by Ivan Pavlov. He found that dogs given meat at regular intervals would salivate toward the end of the interval. The amount of saliva increased as the end of the interval approached. Pavlov said that the waiting period here played the role of the conditioned stimulus to produce a conditioned reflex.

Is there a practical limit to the length of the delay between rewards—a point beyond which temporally regulated behavior will not develop? There is no definitive answer yet. In some of my experiments we failed to obtain good timing in cats with delays beyond eight or 10 minutes. But a number of factors may be involved. The previous experimental history of the cat seems important. And so are the state of deprivation and the nature and amount of reinforcement.

Complexity. If we want to measure timing ability more precisely we can use two levers in the Skinner box. The cat is trained to push the first lever then the second in succession. Then we can introduce a delay: to obtain food the cat will have to push the second lever no less than 30 seconds and no more than 35 seconds after it has pushed the first lever. The time periods can be altered to explore limits of the cat's timing capability.

Or we may want to measure the ability to estimate the duration of a signal. Pavlov conditioned dogs to discriminate between two rhythms of a metronome. Operant-conditioning techniques are somewhat more suitable. You can train an animal to listen to or look at a signal until it stops, and then press a lever for food if it is a long signal and not press the lever if it is a short signal. Or the animal can press one lever after a long signal and another lever after a short signal. By reducing the difference between the two signals we can test the limits of the animal's ability to estimate time duration.

Pastimes. Observing only the temporal behavior of animals can be compared to studying a clock by watching the motion of the hands. Exactly where the organic-clock mechanism is located and how it works has still to be discovered. Some psychologists have noted that some animals fill waiting periods with stereotyped, recurrent behavior. Some rats and monkeys have become famous figures in experimental literature because they bit their tails or turned their heads rhythmically while waiting. But other animals that just rest quietly often display the best regulation of temporal behavior.



CAT IN SKINNER BOX. A cat can learn to estimate time intervals between rewards.

The timing mechanism may perhaps be at a primary physiological level—in muscle-tension changes for example. This hypothesis of acquired temporal regulation was suggested by the French psychologist Pierre Janet 50 years ago and has never been thoroughly explored.

Another hypothesis is that timing behavior depends essentially upon the nervous system. Circadian rhythms have been demonstrated in the nervous structure of a lower organism even when the structure was separated from the rest of the body. Some researchers have conditioned single brain cells to fire at regular intervals. It is an open question whether there is actually a time center in the brain or whether, as Pavlov thought, the ability to estimate time is a general property of the nervous system.

Higher organisms, such as man, do not seem to have better biological rhythms than bees, mushrooms or plants — only more complex. Whether acquired temporal regulation is better in higher organisms needs systematic phyletic studies. Observations at present are rare and fragmentary.

To the laboratory psychologist these problems are interesting in themselves. The researcher today is no less happy at conditioning a cat to press a lever with the regularity of a clock than was the 18th Century botanist at watching flowers continue to open and close according to the daylight-night cycle even in a completely dark cellar.

But the study of acquired temporal behavior has some very practical applications. Some researchers have observed that the regularity of the stress-producing stimuli seems to be responsible for creating neuroses in animals under experimental conditions. Thus, the arbitrary work schedules that are imposed upon modern man may lead to physical and psychological disorders—as may the deadly regularity of assembly-line jobs.

Level. The problem of biological clocks has yet another level—that of subjective time. How is the temporal experience translated into consciousness and symbolic expression? Psychological time is a product of a person's intellectual and affective experiences and is shaped by the cultural environment.

Though some cultures develop explicit philosophies of time, all cultures have implicit philosophies that are expressed in attitudes toward death, in myths, in language and in daily conduct. Time is experienced as perpetual recycling in some cultures, among them those of the Hindus and the American Hopis (brilliantly analyzed by B. L. Whorf).

The Hopi language does not deal with time in the way most European languages do. Whorf found that verbs, for instance, are not arranged in present, past and future tenses. The primary means of characterizing a verb has to do with its validity: whether the speaker refers to a real situation or makes a general statement, etc. Anterior and posterior relationships, as well as duration, come in as secondary characterizations.

The Hopis do not divide time into discrete units that can be added one to the other; rather, they regard time as a repetition of the same event. If days are seen as one recurring event, then how you treat today will have effects on tomorrow. Hopi people emphasize preparation for coming events and believe that by maintaining favorable conditions they can insure the favorable development of later events. A large part of the Hopi religious ritual is focused on these preparations.

Hurry. This is very different from our conception which gives time a starting point and, eventually, an end. We often act as if we were running a race against time—we try to gain time, to do things faster.

Jean Piaget, who studied the origin and development of the conception of time in the child, concludes that there is no primitive intuition of time. At least at the cognitive level, psychological time results from a coordination of distance and speed. (In fact it was a question asked by Albert Einstein about the relativity of time that triggered this part of Piaget's research.)

In a typical experiment Piaget shows a child two small cars. One may travel two feet, the other three feet. They start at the same moment, but the second one travels faster and stops before the first. The child under five thinks that the second car traveled a longer time and he will justify his statement by saying that it traveled a longer distance or went faster. So to the child, faster means more time. Only later can he combine speed and distance into a unitary concept of time. In the same way, when you show a child five pictures in five minutes and then 10 pictures in five minutes, he will say it took more time when there were more pictures. He does not take into account the frequency at which they were shown.

Concept. There is controversy over the relationship between the development of the concept of time and the more elementary biological processes of time regulation. Paul Fraisse, a French psychologist, does not fully agree with Piaget. Fraisse feels that we must consider three separate levels when we analyze biological and psychological time: the level of biological rhythms, the level of direct experience of duration (*temps vécu*), and the level of conceptualization, where cognitive activities affect the concept of time. Though interactions may exist among the three levels they are not essential, and one level does not emerge from the preceding one.

Piaget thinks that there is a continuity from the lowest form of organization to the highest ones. In this case, keeping time, feeling time or thinking time would all result from some sort of coordination between speed and distance, or frequency. Piaget, however, is by choice preoccupied with the highest levels of human behavior, the logical operations. If the speed-distance relationship is not given in the external world, as it may not be in simpler organisms, then it must be assumed that it is given within the organism. And we are sent back to the notion of internal clocks.

Are philosophies of time merely symbolic constructs without any relation to the temporal regulation of the organism? At first sight the two may be very far apart, but the kind of *rapproachment* suggested here, though highly speculative, is not unreasonable. Let me put the problem this way: do physiological and behavioral temporal regulations determine our conscious judgment of time, at least to some extent? And through it, indirectly, our implicit philosophy of time? Such questions may have been purely academic 50 years ago. But they are very practical questions today if we are to predict how man will experience time when he travels into space where he will have to set aside the ancient 24-hour terrestrial cycle and adapt to strange new ones.

Marc Richelle (page 33) feels that his interest in behavioral clocks is an ex-

pression of some deeply rooted preoccupation with time—as a student of philosophy and literature, he chose Marcel Proust and his *Remembrance of Things Past* for a thesis topic.

Richelle received his licence en psychologie in 1955 while studying under Jean Piaget. His doctorate came from the Université de Liège in 1959 after he studied with B. F. Skinner at Harvard in 1958 and 1959. He is now a professor of experimental psychology at Liège.

His studies with Skinner prompted him to establish an operant-conditioning laboratory in Belgium. It was the first of its kind in that country and probably the first in French-speaking Europe.

Richelle is president of the Belgian Psychological Society. He is married and the father of a son and a daughter. Traveling, gardening, writing and a special interest in the French classics occupy his spare time.

Marc Richelle

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