The Economist

BIOCLOCKS

The tyranny of time

People, like all living things, are four dimensional

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IKN SOME respects, it is true, you are the same person at four in the afternoon as at four in the morning. You certainly feel yourself to be the same person. No wonder, then, that for centuries medicine and biology and for that matter philosophy, all following common sense, have assumed that what you do matters far more than what time of day you do it.

Reality, however, appears to be more interesting. The human body is organised not just in three dimensions but in four. The fourth is time. It is not just a part of your environment, a placid daily tide upon which you float. It is an integral part of you.

Species from humans to birds to plants and fungi—even single-cell organisms so primitive that they lack a cell nucleus—possess internal, 24-hour circadian (from the Latin for "around the day") clocks. Certain bacteria with lifespans of only a few hours not only keep time but pass it along to the next generation, so that each is "born" properly oriented to the time of day.

In humans, at 1am post-surgical death is most likely; at 2am peptic ulcers flare up; at 3am blood pressure bottoms out; at 4am asthma is at its worst. When you wake up, your hay fever is at its most tormenting, and in the morning hours, as your blood pressure rises to meet the day, you are most likely to suffer a heart attack or stroke. Your rheumatoid arthritis improves through the day, but your osteoarthritis grows worse. Alcohol is least toxic to the body at around 5pm: cocktail hour.

In 1729, a French astronomer named Jean Jacques d'Ortous de Mairan left his heliotrope plant in the dark and discovered that its leaves continued to open and shut on a regular daily schedule, just as if there had been daylight. So the plant was not merely responding to light; it was regulated by some sort of internal timer. Not much happened by way of building on De Mairan's discovery for nearly 250 years. And then, rather unexpectedly, in 1972 biologists discovered the brain's central clock: a tiny and primitive region called the superchiasmatic nucleus. With an anatomical apparatus now in hand, the field of chronobiology, which maps the junctions between life and time, was born.

Today the study of circadian rhythms occupies thousands of researchers in life sciences as diverse as genetics, psychiatry, pharmacology and animal husbandry. They are finding that time is a constituent element of life, and that understanding it this way is a key that opens many doors.

At the University of Virginia, Michael Menaker has spent years studying the biological time-keeping of a small menagerie of animals. The retinas of lampreys and iguanas, and also of hamsters and frogs and other creatures, contain clock cells. Dr Menaker harvests the cells, keeps them alive in nutrient solutions, and then monitors their ticking. When he plots these various animals' clock rhythms, he finds remarkably similar daily patterns.

"Lampreys, as you may remember from your intro biology course," he says, "are the most primitive vertebrates that we can get hold of, and they separated from the rest of the vertebrates 450m years ago. So—and this is really important to us—anything that was common to lampreys and other vertebrates has been maintained for 450m years."

This seems logical. Feeding, for example, might be difficult and metabolically expensive in the dark and cold of night. Even a very primitive organism might fare better if its body "knew" the best time to seek food. A clock, then, might well have been devised early in life's history, and then preserved and refined.

In the 1990s, after years in which little progress was made, the mechanism has rapidly emerged into view. It works like a water clock, in which a bowl gradually fills until at last it tips, beginning a new cycle.

In an analogous fashion, clock genes construct proteins which eventually accumulate to the point where they switch off the genes. The cycle takes 24 hours.

In one important respect the gene discoveries point in the same direction as Dr Menaker's study of animals: the same genes that run the clocks of fruit flies are also turning up in mammals, including humans. "There aren't many things that are that universal in life," Dr Menaker explains. "It's mostly a tremendous amount of variability." The fact that such genes seem to be so common suggests that the circadian clock is both very old and very valuable.

In 1997, a group of researchers at the Scripps Research Institute and Brandeis University, in America, further deepened the picture. By inserting some firefly genes into a fruit fly, they created a mutant whose body glowed wherever its clock genes were active. The researchers were astonished to find clocks ticking all over the fly's body—in the wings, the legs, the proboscis. The fly was a veritable clock shop. Zebra fish and rats, other researchers have recently found, also express clock genes around their bodies. And humans? As though in partial answer, in 1998 researchers at America's Cornell University were flabbergasted when they made the strange discovery that humans' body clocks could be reset by shining bright light on the back of the knees. Although that experiment has yet to be replicated, the science looked good. At this point, no one will be surprised if people turn out to be clock shops.

Assembling these clues suggests several inferences. First, time-keepers are fundamental and ubiquitous in living things, rather than merely incidental and isolated. Second, there may be any number of respects—not all of them obvious—in which life forms, including human beings, change as the hours go by. Third: learn to manipulate or exploit those rhythms, and you may hold a powerful therapeutic tool.

Time for your medicine

Time is invisible and it is free. It cannot be bottled or patented. Commercial pharmaceutical firms have not shown a great deal of interest in it, and even today few doctors give it a second thought. Yet in the 1980s tantalising evidence began to appear, suggesting that time matters a great deal when it comes to treating disease.

In 1985 an American oncologist named William Hrushesky published a paper in the magazine *Science* reporting what happened when he switched the timing of chemotherapy in 31 women who had ovarian cancer. Then, as now, the usual method was simply to administer chemotherapy in a steady dosage as quickly as possible, without regard to the time of day. Dr Hrushesky, however, guessed that if people's cells follow a cycle every day of faster and slower growth, then the body's toleration of poison—which is what chemotherapy is—may fluctuate. Cancer cells' susceptibility to poison might also fluctuate, he speculated.

So in his trial Dr Hrushesky divided the women into two groups. Each group received two standard cancer drugs, but Dr Hrushesky fiddled with the times the drugs were administered, so that one group's daily schedule was the inverse of the other. He found that the women on one schedule developed roughly half the side effects of the women on the other, with fewer treatment delays. There was less hair loss, less nerve damage, less kidney damage, less bleeding, fewer transfusions: "Every toxicity was markedly diminished several-fold simply depending on what time of day the drugs were given," Dr Hrushesky says.

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At about the same time, working independently of Dr Hrushesky, Francis Lévi began using chronotherapy to treat cancer patients in France. Today Dr Lévi, at the Hôpital Paul Brousse just south of Paris, and his associates at more than 30 clinical centres around Europe, routinely equip their colon-cancer patients—1,500 of them to date—with a small computerised pump about the size of three or four compact discs. The pump connects to a port in a vein, and is programmed to infuse medication so as to oscillate gradually upward and then back down over the course of the day (the precise schedule depends on the drug).

In 1999, Dr Lévi and his associates published the results of a multi-centre trial in which time-pumps were used to treat 90 colon-cancer patients at ten clinical centres in France, Italy, Belgium and Canada. The researchers found they could push the dosage of chemotherapy much higher than the maximum that the body can tolerate under a flat-rate regime, and they attained about a three-fold increase in the

proportion of tumors that shrank by half or more. That was consistent with results Dr Lévi and his colleagues had published in 1994 and 1997, when they compared chronotherapy with flat dosing. "All the side effects are reduced by chronotherapy," says Dr Lévi. "And this despite the fact that the dose which could be delivered was higher by 40%."

Certainly dosage and timing are related for asthma patients, whose number has doubled since 1975 in America alone (to 15m). The majority of asthma patients suffer most at night, possibly because that is when cortisol, the body's natural anti-inflammatory, is at its lowest level. The most common time for an attack is 4am, so the agony of the asthma itself is often compounded by the further strain of sleeplessness.

In Denver, at the National Jewish Medical and Research Centre, researchers are spreading the word that a dose of asthma medicine taken at 8pm, or at 8am, is not the same as a dose taken at 3pm, when it is likely to be much more effective. When asked why, Monica Kraft, the director of the centre's pulmonary physiology unit, explains that dosing at 3pm allows the medicine to reach the afflicted cells just when they most need it, rather than pushing against the body's circadian tide. Dr Kraft remembers a call she received from another physician, whose asthmatic daughter was awakened by nightly attacks. After changing the dosing time (and making a few other changes), the girl was able to sleep through the night—no small blessing, if you have chronic asthma.

Blood pressure is markedly circadian. It rises quickly in the morning, which is why heart attacks and angina are most likely then. At the University of Connecticut's school of medicine, William White notes that treating high blood pressure with a constant dose of medication could push blood pressure too low at night without reducing it sufficiently in the morning. Two time-delayed drugs for blood pressure (Searle Pharmaceuticals' Covera-HS and Schwarz Pharma's Verelan PM) are now on the market: patients take them before bedtime, but the drugs kick in shortly before the patients awake. They are the first major commercial drugs that exploit circadian rhythms. More may follow in the next couple of years, when the first large international trial of chronotherapy, involving 15 countries and 17,000 blood-pressure patients, is completed.

Blood pressure and cancer may only be the beginning. Many types of inflammation, pain, arthritis, and other afflictions also seem to follow daily cycles. A decade or two hence, a casual attitude about the timing of medical treatment may seem as benighted as a casual attitude about dosing seems today. Time, true, is a tool whose very ordinariness seems to belie its power. Yet in some cases its power can be astonishing, at least to those who experience it.

Riding rhythms

In 1957, when he was still attending university, Charles B suffered the first in a series of black depressions—so debilitating that he asked that his name be withheld, so as not to alarm his clients (he is an American in a profession that requires intimacy and trust). The depression was worst in the morning and lifted, to an extent, as the day went on. "It's a feeling of foreboding, it's blackness, it's hopelessness, guilt, a feeling of failure," he says. "It's a feeling like being on the 50th floor of a building outside a window, just sort of hanging on with one's fingernails, feeling that one was about to be consumed by the void." Neither psychological therapy nor drugs did any good. At last he heard of a doctor named Thomas Wehr, and went to him for help.

Dr Wehr, besides being a practising psychiatrist, is chief of the section on biological rhythms at America's National Institute of Mental Health. The fact that Charles B's depressions lifted during the day suggested that circadian rhythms might be at work. As it happened, Dr Wehr's research had led him to explore the ways in which manipulating sleep can help some people ride the body's rhythms upward and out of depression. "It's not only the amount of sleep that's influencing the mood of these patients, but the timing of sleep," Dr Wehr says. "If you're awake in the latter part of the night, that seems to have an anti-depressive effect."

That sleep and depression are intimately related has been known for years. In 1971, two German researchers reported that a sleepless night had transformed a depressed patient. Subsequent research, although desultory, showed that 60% or more of depressives respond—often dramatically—to a night of sleep deprivation, and that the transformation of mood usually occurs in the latter half of the night. "It's a remarkable phenomenon," says Dr Wehr. "The patient could have been withdrawn and depressed and hopeless and tearful and unexpressive and pessimistic for months, and we ask them to stay awake all

night. The next morning I would come in and be greeted at the door by someone who's very talkative and very excited. Once you've seen it, you never forget it."

The trouble is that everyone needs to sleep, and even a short morning nap after a sleepless night brings the depression roaring back. Something interesting is going on, clearly; but how could the effects be made more than fleeting?

In Germany, at the hospital of the University of Freiburg, Mathias Berger has recently concluded the first controlled trial of its kind that suggests an answer. He began with 40 depressed patients who had been successfully lifted from their depression by a night without sleep. The next day, half of these patients were put to bed six hours earlier than normal. They slept from 5pm to midnight, so that they were awake through the early-morning hours. Then their bedtime was delayed an hour each night, until after a week they were back to a normal bedtime (11 pm). The result was that three-quarters of the treated group did not relapse into depression: a success rate twice as high as that of the 20 patients in the control group, who received a placebo regimen.

In other words, the anti-depressive effects of sleep manipulation can be sustained. "These patients had had depression for months," says Dr Berger. "It shows—and this is the most important aspect for me of this study—that there is no holy law of nature that you can improve depressive patients only within three or four weeks, as anti-depressive drugs are able to do."

Just what is going on? As with so much in the infant field of chronotherapy, theory lags practice. Dr Wehr suspects that the effect may have to do with a surge, during the wee hours, of certain hormones associated with the thyroid. If you are awake through the latter part of the night, he says, "that surge just takes off and goes. So this is a kind of trick for flogging the brain and the pituitary and the thyroid to dump out a lot of their respective hormones. It's kind of like using your body as its own pharmacy."

No other sort of pharmacy had worked for Charles B, who was desperate by the time he found Dr Wehr. Noticing the circadian pattern of Charles B's depression, Dr Wehr asked him to get through a night without sleeping, and then to increase his nightly sleep only gradually, so that for almost a week he was awake during those crucial early-morning hours. The first trial's effects quickly dissipated. (Response to sleep manipulation—as, for that matter, to drugs—is often inconsistent.) A second try was aborted when Charles B overslept.

But the wonder still rings in his voice when he describes the third try. "Over the course of the night I just physically felt better. You can feel it, like it comes from your insides." It felt as though someone had given him a powerful mood-altering injection. By morning he felt fine. Little by little he added sleep each night, fearing that the good news might not last. But it did. The depression was gone. He fears its return, of course, but much less than before. Now he has a weapon.

The fourth dimension

The point is not that sleep manipulation is a cure for depression or that drugs can be thrown away (to the contrary: the technique works in harmony with drugs, which can help sustain the effect). Nor, for that matter, is the point that timing chemotherapy to trace the body's rhythms is a cure for cancer. It is not. The point, rather, is that the new century finds people on the doorstep of a new way of thinking about themselves, a way that points to research agendas and therapeutic strategies where before there was only the ephemeral ticking of the clock.

The deep integration of time into science's model of human life—indeed, of all life—is only just beginning; its uses almost all await discovery. At bottom, however, chronobiology is most important, not for any particular application, but as a way of reconceiving the structure of life. "Living beings are organised in time every bit as much as they're organised in space," Dr Menaker says, "and temporal organisation has been neglected relative to spatial organisation." As the balance begins to be rectified, humans and other creatures become, at last, fully four-dimensional.

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