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Enter, the Chronotherapists

By *OLIVIA JUDSON*

Olivia Judson on the influence of science and biology on modern life.

Tags:

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Here's my prediction for the Next Big Thing in health care: chronotherapy, or therapy by the clock. Yes, in the future, your medicines, your operations, your mealtimes and when you step onto the treadmill or the badminton court — all will be overseen by your personal chronoconsultant.

It's been known for ages that our bodies have daily, or "circadian," rhythms. Body temperature is lower in the morning than it is in the afternoon. Blood pressure is low during the night, and rises just before you wake. Muscles are stronger in the afternoon than they are in the morning, and you may have greater dexterity then, too. Badminton players tend to serve more accurately in the afternoon, for example.

But now it's clear that the body clock is in charge of many other, more subtle processes as well. The content of human breast milk changes during the day. Evening milk is full of compounds that make a baby sleepy; morning milk isn't. The liver, too, has a strong daily rhythm: many of its activities shut down during the night. Levels of several hormones, including melatonin (involved in sleep) and ghrelin (involved in appetite), rise at night. Testosterone, in contrast, is highest in the morning and lowest in the late afternoon. Cholesterol is made more rapidly at night. Even cancers have a rhythm: breast cancers, for instance, grow faster during the day.

The implications of all this are huge. Living against your body clock — as so many of us do — can affect your health and well-being in myriad ways. Some of these are trivial: unless you're professional (or super-competitive), it probably doesn't matter if your badminton serve is a little off in your morning games. Besides, your opponent's will be, too. (It may, however, be better for your heart if you play in the afternoon.)

But living against the clock can also lead to major health problems. Obesity, breast cancer and certain kinds of mental illness are all associated with circadian disruption.

Disruption can be a consequence of shiftwork or jetlag — or of not spending enough time sleeping, or in the dark. Darkness is important because even a brief exposure to light

during sleep-time can be enough to reduce melatonin levels and reset the body clock. Exposure to light in the night has been linked to breast cancer; consistent with this, women who are totally blind have a lower incidence of breast cancer than those who can see even a little bit.

Badly timed light isn't the only troublemaker. Eating at the wrong moments — like the middle of the night — makes it harder for the body to process food and leads to weight gain. A recent experiment shows this nicely. Two groups of mice were fed identical diets but on different schedules: one group was allowed to eat only during normal waking hours, while the other was restricted to eating during normal sleeping hours. After six weeks, the mice allowed to eat only during sleep-time were significantly fatter than the wake-time eaters — a result that may help explain why obesity is so common among shift-workers who, because of their jobs, are forced to eat against their clocks.

In fact, sleep itself has been implicated in obesity: not sleeping enough is associated with getting fat. (Which suggests the sleep diet: stack those Zs and see the pounds melt away!) More worrying: obesity may actually interfere with the clock mechanism. In mice, the genes involved in regulating the body clock function differently in obese animals as compared to thin ones: the clocks of obese animals are less rhythmic. Perhaps, then, one way to treat (or prevent) obesity would be to impose a strong circadian rhythm on mealtimes and bedtimes.

To my knowledge, chronotherapy has not yet been tried for obesity; but it has, with great success, been used in psychiatry. Several mental disorders, including bipolar disorder, can be rapidly ameliorated by a resetting of the body clock. Indeed, it's been argued that manipulating the body clock affects the same parts of the brain as antidepressant drugs — but that chronotherapy works faster and with fewer side effects.

Even conventional medicines work better when the body clock is taken into account. For example, evidence suggests that some statins — drugs that help people reduce their cholesterol levels — are more effective when taken before bedtime. Several of the drugs used in chemotherapy also have a “best” time of day: give the drug at the right moment, and you can take a smaller dosage, get a greater benefit and have a lower risk of unpleasant side effects. Sounds good. But don't forget: regular good sleep in a nice dark room can inhibit tumors, and may thus help you avoid chemo in the first place.

Much more, no doubt, remains to be discovered, and it may, in fact, be a while before a chronotherapist opens an office near you. (That's often the nature of the Next Big Thing — you see it on the horizon ages before it arrives.) But while we're waiting for medicine by the hourglass, there are still steps that can be taken. I don't know about you, but I'm going to darken my bedroom, cancel the midnight feasts and put sleep at the top of my list of things to do. It's about time.

Notes:

The circadian rhythm of body temperature is well known — and easy to verify for oneself. For the circadian rhythm of blood pressure, see Smolensky, M. H. et al. 2007. “Role of sleep-wake cycle on blood pressure circadian rhythms and hypertension.” Sleep Medicine 8: 668-680. For an overview of muscle strength being higher in the afternoon, see Reilly, T. and Waterhouse, J. 2009. “Sports performance: is there evidence that the body clock plays a role?” European Journal of Applied Physiology 106: 321-332; see also the references therein. For badminton serves being better in the afternoon, see Edwards, B. J., Lindsay, K. and Waterhouse, J. 2005. “Effect of time of day on the accuracy and consistency of the badminton serve.” Ergonomics 48: 1488-1498.

For the content of breast milk fluctuating through the day, see Sánchez, C. L. et al. 2009. “The possible role of human milk nucleotides as sleep inducers.” Nutritional Neuroscience 12: 2-8; and Cubero, J. et al. 2005. “The circadian rhythm of tryptophan in breast milk affects the rhythms of 6-sulfatoxymelatonin and sleep in newborn.” Neuroendocrinology Letters 26: 657-661. For the liver having a strong circadian rhythm, see Reddy, A. B. et al. 2006. “Circadian orchestration of the hepatic proteome.” Current Biology 16: 1107-1115. The behavior of melatonin is well-known; but for a good overview of how it works, see Blask, D. E. 2008. “Melatonin, sleep disturbance and cancer risk.” Sleep Medicine Reviews 13: 257-264. This paper also reviews the association between cancers and shift-work, and between cancers and exposure to light at night. The author also advocates spending time sleeping and in total darkness as a possible anti-cancer therapy.

For ghrelin being higher at night, see Yildiz, B. O. et al. 2004. “Alterations in the dynamics of circulating ghrelin, adiponectin, and leptin in human obesity.” Proceedings of the National Academy of Sciences USA 101: 10434-10439. For testosterone being higher in the morning, see Brambilla, D. J. et al. 2009. “The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men.” Journal of Clinical Endocrinology and Metabolism 94: 907-913. For cholesterol synthesis, see the paper by Crispim et al. 2007, listed below. For breast cancers growing more during the day, see Brainard, G. C. et al. 2005. “Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats.” Cancer Research 65: 11174-11184.

For a review of light-at-night as a risk factor for breast cancer see, for example, Stevens, R. G. 2009. “Light-at-night, circadian disruption and breast cancer: assessment of existing evidence.” International Journal of Epidemiology 38: 963-970. For blindness and breast cancer see, for example, Flynn-Evans, E. E. et al. 2009. “Total visual blindness is protective against breast cancer.” Cancer Causes and Control 20: 1753-1756.

For obesity and circadian disruptions, see Laposky, A. D. et al. 2008. "Sleep and circadian rhythms: key components in the regulation of energy metabolism." FEBS Letters 582: 142-151. For mice gaining weight when they eat during sleep time, see Arble, D. M. et al. 2009. "Circadian timing of food intake contributes to weight gain." Obesity 17: 2100-2102.

For sleep deprivation being a risk factor in obesity see, for example, Crispim, C. A. et al. 2007. "The influence of sleep and sleep loss upon food intake and metabolism." Nutrition Research Reviews 20: 195-212; also see this paper for a review of the circadian rhythm of cholesterol synthesis. These authors argue for more sleep as one way to help prevent obesity.

For obesity interfering with the body clock in mice, see Kaneko, K. et al. 2009. "Obesity alters circadian expressions of molecular clock genes in the brainstem." Brain Research 1263: 58-68. A google search on "chrononutrition" reveals a French diet that purports to work by timing food consumption; however, I was unable to find any papers about it in the standard scientific databases, so I couldn't assess how well it works.

For the treatment of psychiatric disorders by means of chronotherapy, see Wirz-Justic, A. 2009. "From the basic neuroscience of circadian clock function to light therapy for depression: On the emergence of chronotherapeutics." Journal of Affective Disorders 116: 159-160. See also Benedetti, F. et al. 2007. "Chronotherapeutics in a psychiatric ward." Sleep Medicine Reviews 11: 509-522. A treatment manual is also now available: see <http://www.chronotherapeutics.org/Index.html>.

For statins and time of day, see Plakogiannis, R. and Cohen, H. 2007. "Optimal low-density lipoprotein cholesterol lowering: Morning versus evening statin administration." Annals of Pharmacotherapy 41: 106-110. For time of day and chemotherapy, see Kobayashi, M., Wood, P. A. and Hrushesky, W. J. M. 2002. "Circadian chemotherapy for gynecological and genitourinary cancers." Chronobiology International 19: 237-251. See also Mormont, M.-C. and Levi, F. 2003. "Cancer chronotherapy: Principles, applications, and perspectives." Cancer 97: 155-169.

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