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The Wild Side
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Guest Column: Who Put the Lag in Jet Lag?

Many thanks to Sandra Aamodt and Sam Wang for a marvelous series of articles. Next up: Leon Kreitzman, an authority on questions of the body clock, like why jet lag happens and why teenagers aren't lazy just because they sleep late. Please welcome him.

Before I hand over to him, however, I'd like to pay a brief tribute to Sir John Maddox, one of the first science journalists and a long-serving and hugely influential editor of the journal Nature. He died at the weekend, and will be much missed by the scientific community.

Now: Leon!

— Olivia

By Leon Kreitzman

The Japanese call it Jisaboke and in French it is les effets du décalage horaire. Whatever the language, the symptoms of jet lag are the same the world over — fatigue, insomnia, disorientation, swelling limbs, loss of appetite, headaches, mood disturbances, bowel irregularity and light-headedness. Jet lag has also been implicated in loss of libido, nausea, sore throat, fall in cognitive performance and even an increased susceptibility to malaria.

It is not just unpleasant. Jet lag can start wars. In 1956, United States Secretary of State John Foster Dulles arrived back in Washington after a long flight to learn that the Egyptians had just bought a substantial amount of Russian arms. Dulles immediately canceled the agreement he had made with Colonel Nasser to bankroll the Aswan Dam project. The Suez Crisis that followed ended Britain's imperial pretensions, and at the height of the Cold War the Russians had their first foothold in Africa.

Years later Dulles admitted that he had made a mistake in acting so hastily. He blamed it on the effects of jet lag.

During his state visit to China, President George W. Bush blamed jet lag when he couldn't find which door to use to get off the stage. President Obama looked as though he could have used a couple of days off before the start of the G-20 (though his wife looked great).

Unsurprisingly, Britain's Iron Lady took jet lag in stride. About to fly off to Japan for an economic summit, Prime Minister Margaret Thatcher said, "Jet lag is an awful nuisance when you're going straight into talks and negotiations, but we'll cope . . . we'll cope all right." And she did.

When we fly across more than three or four time zones many of us get one or more jet lag symptoms, depending on how far we fly, the direction in which we are heading (most people find it easier to deal with jet lag when flying east to west, chasing the sun) and the time of departure. The more time zones we cross, the longer it takes for the body to adjust to its new time patterns.

Practice does not help. Long-haul airline pilots who are continually flying halfway around the world and back generally feel out of sorts most of the time. Company executives who spend more time in the air than in the office never really adjust, even when they adopt the Lyndon Johnson strategy and try to pretend that nothing has changed and resolutely refuse to reset their watches to local time. American tennis players reckon they need to allow at least a week to get their body clocks back into gear when they fly from the U.S. to England for Wimbledon.

Jet lag comes courtesy of a disruption in your body's internal clocks, a condition known as circadian desynchronization. Nearly every living creature has a circadian system whose rhythms control the timing of many aspects of biochemistry, physiology and behavior. For instance, virtually all our hormones

oscillate with a 24-hour rhythm. Our body temperature falls at night and rises in the day. Other examples of human rhythmic physiology influenced by the circadian system include heart rate, blood pressure and the sleep-wake cycle.

In mammals, the rhythmic source was thought to be localized in a small paired structure of some 16,000 neurones called the suprachiasmatic nuclei (SCN) in the anterior hypothalamus of the brain. The SCN neurones individually are capable of generating near-24-hour oscillations in electrical activity and, collectively, they produce the master rhythm that essentially controls the animal's crucial rest-activity cycle.

The SCN-generated rhythm is aligned to the daily solar cycle of 24 hours by the photic signals of sunrise and sunset via a light-sensing pigment called melanopsin, found in special cells located in the retina of the eye.

We know now that as well as the SCN, mammalian tissue cells like the liver, kidneys and heart (though notably not the testes) have their own circadian clocks. Put crudely, if rat liver cells are kept alive in a dish for several days, we can still measure a near-24-hour cycle in the activity of genes that code for proteins that have a specific enzyme function in the liver, like alcohol dehydrogenase.

Alcohol dehydrogenase production peaks in the late evening, which is why we can drink more alcohol then than in the morning. About one-fifth of liver enzymes show circadian rhythms, according to Dr. Michael Hastings of Cambridge University. This means that the metabolic capabilities of the liver change dramatically between day and night as different groups of enzymes are turned on and off.

Regulating the production of liver enzymes up and down in a timed sequence enables the liver to do its metabolic job more efficiently. But left to their own devices, the liver's clocks can fall out of sync with the clocks in other tissues. The SCN signals inform the peripheral cells to adjust the phase of their rhythms, like the pin of a wrist watch being moved a little bit forward or backward.

If we think of the circadian system as an orchestra, then the SCN, synchronized to the external world by the light signals, acts like the conductor, beating out a rhythm that coordinates the multiple rhythmic parts of the body. When the orchestra is in time we get a melody; when it is not there is a cacophony. The same thing happens in our bodies, though how this is done is not at all clear and is the subject of intensive study.

Crossing time zones in a jet plane decouples these rhythms from the natural day-night cycle. (Astronauts in orbit may see 16 dawns and dusks in 24 hours, so it is no wonder that sleeping tablets are the most frequently used medication in space.) On a long trip, the various rhythms fall out of sync and your stomach ends up over Peking, your liver somewhere near Delhi, while your heart is still in San Francisco. Metaphorically speaking, of course.

To counteract jet lag, weary travelers can pick from any number of measures. Some people use special diets; others tap the meridian lines of Chinese medicine every hour or so in flight. Henry Kissinger apparently used to prepare for long flights by adjusting his pre-flight sleep and wake times in the hope of ameliorating the jet lag symptoms.

Melatonin is a popular remedy, though there are considerable doubts as to whether there is much in the way of benefit. Depending on the length of the journey, direction of travel and landing time, seeking (or avoiding) sunlight on landing so as to shift the clocks into alignment with local time is favored by at least one top researcher.

Whether any or all of these methods work seems to depend as much on the faith put in the remedy as to any rational basis.

Help, however, may be at hand thanks to some recent studies on "jet lagged" mice. Giles Duffield of the University of Notre Dame, in conjunction with colleagues at Dartmouth Medical School and Norris Cotton Cancer Center, monitored mice over several weeks, under different light/dark schedules, recording mice activity day and night via electronically rigged running wheels.

Altering the lighting schedules caused a 10-hour delay in the usual mouse circadian cycle, equivalent to a person flying from Athens to Los Angeles. Normal mice took about four or five days to return to their usual activity routine. But genetically engineered mice lacking the Id2 gene adapted twice as fast and were back on their normal running-wheel rhythm in only one to two days.

It goes without saying that mice and humans are different, and as the Id2 gene is important in fetal development, messing with it may be tricky. The study does give a glimpse as to possible ways to cure jet lag by somehow manipulating the gene so as to rapidly adjust our internal clocks and get rid of the lag. But just because we can does not mean we should.

While a scientifically based solution may be bad news for the jet lag remedy business, making long-haul flights easier may not be such a good idea if we are keen to reduce CO2 emissions.

Maybe the answer is to develop two pills. One would inhibit jet lag symptoms and would be available to all essential long-haul fliers like pilots and, say, academics attending conferences. Non-essential long-haul travelers would have to take another pill, which would *intensify* the effects of jet lag. They could still fly if they wanted to, but most would not and we essential travelers would, at last, be able to stretch out in comfort.

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NOTES:

"The Jet Lag Book" (Futura 1984), by Don Kowet

For a description of peripheral clocks in the liver see "Circadian Orchestration of the Hepatic Proteome," Akhilesh B. Reddy, Natasha A. Karp, Elizabeth S. Maywood, Elizabeth A. Sage, Michael Deery, John S. O'Neill, Gabriel K.Y. Wong, Jo Chesham, Mark Odell, Kathryn S. Lilley, Charalambos P. Kyriacou, Michael H. Hastings Current Biology — 6 June 2006 (Vol. 16, Issue 11, pp. 1107-1115)

For the study of "jet lagged" mice see Giles E. Duffield, Nathan P. Watson, Akio Mantani, Stuart N. Peirson, Maricela Robles-Murguia, Jennifer J. Loros, Mark A. Israel, Jay C. Dunlap. "A Role for Id2 in Regulating Photic Entrainment of the Mammalian Circadian System." Current Biology, 2009; 19 (4): 297

Charles Ehret attests to Kissinger's schedule in "Overcoming Jet Lag" (Berkley Publishing Group, 1993)

The connection between jet lag and malaria is from a paper by C. Jairaj Kumar, "Jet lag and enhanced susceptibility to malaria Medical Hypotheses" (2006) 66, 671–685. It is based on Kumar's claim that "It is often seen that the jet-lagged individuals who visit their family and friends in areas endemic to malaria have an enhanced susceptibility to malarial infection than the local residents." It is based on the diurnal rhythm of itch sensitivity in humans, which ought to be sufficient teaser to go read the paper.