Jet Lag

Almost everyone who has traveled across more than a few times zones in one trip has experienced the debilitating effects of jet lag. While travel across vast distances is now rapid, convenient, and commonplace, we are still saddled with biological limitations arising from millions of years of evolution. The distress associated with jet lag results when the body's internal clock, or circadian rhythm, becomes desynchronized with the external time zone.

Jet lag is characterized by unpleasant symptoms, including insomnia, sleepiness, impaired performance, diminished alertness, irritability, depressed mood, and gastrointestinal distress (Waterhouse J et al 2005). The symptoms of jet lag are slightly more dramatic for travelers heading east. In addition, older individuals are likely to suffer more from its effects (Monk TH 2005).

The human circadian rhythm—characterized by rising and falling hormone levels, undulating body temperature, and the familiar sleep-wake cycle—is linked to the rising and setting of the sun. Through its production of melatonin, the circadian hormone, the pineal gland plays a crucial role in the circadian rhythm.

Research suggests that the jet aircraft environment itself may also contribute to jet lag. In a recent experiment, researchers simulated the mild oxygen deprivation, or hypoxia, that occurs in pressurized aircraft cabins during long-duration flights at altitudes between 8000 and 12,000 feet. Participants were assessed for changes in melatonin levels. Scientists found a significant decrease in the nightly peak of melatonin, prompting speculation that hypoxia induced by cabin air contributes to post-flight fatigue after long flights and to the clinical disorder of jet lag (Coste O et al 2004).

JET LAG'S EFFECTS ON THE MIND AND BODY

Symptoms of jet lag may include malaise, decreased strength and efficiency, decreased ability to remember or concentrate, gastrointestinal disturbance, headache, irritability, loss of appetite, tiredness during the day, and sleeplessness at night (Committee to Advise on Tropical Medicine and Travel 2003; Haimov I et al 1999; Katz G et al 2001; Lemmer B et al 2002; Nicholson AN et al 1993; Waterhouse J et al 2005b). Scientists have documented that even elite athletes' performance suffers from jet lag, and some globetrotters may experience depression after long flights (Boivin DB et al 2002; Cardinali DP et al 2002; Lemmer B et al 2002; Reilly T et al 2005).

Researchers have documented that jet lag affects the normal daily changes in blood pressure and heart rate, alters otherwise normal changes in body temperature, and disrupts the normal ebb and flow of the stress hormone, cortisol. These alterations in normal functions may last for a week or more (Cho K et al 2000; Lemmer B et al 2002; Tateishi O et al 2002). For instance, long-distance flight crews experiencing chronic jet lag, may have significantly elevated cortisol levels compared to those of controls. This elevation in cortisol correlates with deficits in cognitive performance (Cho K et al 2000).

In addition, jet lag may trigger more serious conditions (Katz G et al 2002). Researchers in Israel have investigated the relationship between jet lag and major psychiatric disorders. Conducted at a mental health center at Hebrew University in Jerusalem, the study involved 152 patients who had been hospitalized for psychiatric disorders within a six-year period. Researchers assigned patients to one of two groups, based on the number of time zones they had crossed while traveling to Israel. Only patients who were mentally healthy at the time of travel or who had been free of any psychiatric symptoms for at least one year before travel were included in the study. The team documented a significant correlation between crossing seven or more time zones and a relapse of psychiatric disorders (Katz G et al 2001, 2002).

Researchers in France have investigated whether chronic disruptions of the circadian rhythm could hasten cancer growth. Working with mice, they entrained one group to a normal rhythm of 12 hours' daylight followed by 12 hours of dark. A second group of rodents repeatedly underwent 8-hour advances of the light-dark cycle every two days. Both groups were injected with cancerous cells known to cause tumors in mice. Compared with the mice kept on a normal sleep-wake cycle, the jet-lagged mice experienced faster tumor growth (Filipski E et al 2004).

Among humans, scientists have observed that frequently jet-lagged individuals and night-shift workers whose circadian cycles are routinely disrupted are more prone to disease than are people who adhere to a normal sleep-wake cycle. Shift workers, for instance, are at increased risk of experiencing cardiovascular, gastrointestinal, and reproductive dysfunction, and they are more prone to developing clinical depression (Burch JB et al 2005; Knutsson A 2003; Moore-Ede MC et al 1985; MurataK et al 1999; Reddy AB et al 2002, 2005; Scott AJ 2000). There is also a correlation between sleep and proper immune function, so insomnia related to jet lag may increase susceptibility to infection (Bariga-Ibars C et al 2005).

COMBATING JET LAG WITH MELATONIN

Most scientifically sound methods for reducing the effects of jet lag are based on two facts:

1. In healthy individuals, circadian rhythm is synchronized with daylight.
2. The effects of the daylight-dark cycle on the circadian cycle are mediated by melatonin.

Specifically, melatonin is secreted by the pineal gland in response to the absence of light. Melatonin triggers a cascade of chemical and physiological responses that ultimately result in sleep, usually within about 30 minutes. As dawn breaks and light begins to impinge on the brain's “circadian pacemaker,” melatonin production drops off dramatically, and the waking portion of the daily sleep-wake cycle begins.

Strategies to manipulate the sleep-wake cycle, such as those used to alleviate symptoms of jet lag, therefore depend on the strategic manipulation of exposure to bright light and the intake of supplemental melatonin at key times. Some studies have also examined the usefulness of stimulants such as caffeine.

JET LAG: A DANGEROUS DEFICIENCY IN MELATONIN

Melatonin's role in human health is far more profound than was once suspected. We now know that melatonin has remarkable properties as an antioxidant and as a modulator of immune system functioning. As an antioxidant, it works on several levels. Production of the body's natural antioxidant enzymes, such as the superoxide dismutases, peroxidases, catalase, and glutathione peroxidase, is promoted by melatonin. On the other hand, melatonin triggers other cell-signaling pathways that result in decreased production of harmful, inflammation-producing chemicals, such as nitric oxide synthases and lipoxygenases.

Receptors for the melatonin molecule are found throughout the body, including the gastrointestinal and reproductive tracts, and it is now known that melatonin is produced by a number of tissues, including skin, gut, liver, kidney, and white blood cells (Hardeland et al 2005b; Iwasaki S et al 2005; Kvetnoy I 2002).

Another recently published study examined the effects on the skin of laboratory rodents after removing their pineal gland. Changes in skin thickness and texture, among other changes, were seen in animals whose pineal glands had been removed but not in control animals that had undergone a sham operation. When supplemental melatonin was given to the affected rodents, their skin dramatically improved. These results suggest that melatonin is a highly efficient antiaging factor and, as its levels decrease with age, melatonin treatment may reduce age-related skin changes (Esrefoglu M et al 2005).

Other studies have suggested that melatonin plays an important role in preserving neurological function in spinal cord injuries to rats (Gul S et al 2005; Liu JB et al 2004). In fact, melatonin is under investigation as a treatment for age-associated neurological disorders such as Alzheimer's disease (Srinivasan V et al 2005). Some of its metabolites are believed to improve mitochondrial functioning and quell inflammation (Hardeland R et al 2005a).

Thus, melatonin plays an indispensable role in synchronizing the body's internal clock with the external environment and is also a vital component of overall health and well-being (Claustrat B et al 2005). Jet lag, which involves a disruption not only of the sleep-wake cycle but of melatonin secretion as well, is not to be underestimated as a potential threat to health.

THE “CHRONOSENSE”: AN INTERNAL TIMEKEEPER

Melatonin, which stimulates sleep, is only part of the equation when it comes to jet lag. Light is also a major factor in regulating the natural circadian clock. German researchers have proposed a previously unsuspected role for the eye in the function of the circadian clock. While the structure and function of the eye as the sensory organ of vision are well known, the eye apparently also serves as an organ of time sense (Erren TC et al 2004).

This role relies on a sensory pigment that allows non-image-forming photoreception in mammals. The researchers refer to the nexus of this photopigment and the retinal nerve as the “chronoreceptor,” which mediates the sense of time, or “chronosense.” Although the exact photopigment responsible for chronoreception has not yet been identified with certainty, a chemical called melanopsin is emerging as a likely candidate (Erren TC et al 2004; Silva MM et al 2005; Fu Y et al 2005).

These newly discovered chronoreceptors provide the brain with readings that correspond to changes in the intensity of both natural and artificial light. These light signals travel from the eye through a small subset of retinal ganglion cells to a region of the hypothalamus (specifically, to the suprachiasmatic nucleus), and from there to the pineal gland. The suprachiasmatic nucleus is also the site of the circadian pacemaker.

Recently, scientists in Brazil demonstrated that the chronosense, or light-dark entrainment, occurs even in blind primates that are otherwise unresponsive to visible light. This finding suggests the biological importance of adjusting the circadian rhythm to the daily light-dark cycle (Silva MM et al 2005). As further evidence of the importance of the chronosense, researchers discovered recently that newborns are functionally blind at birth, yet the newborn retina is nevertheless sensitive to light, and there is a functioning connection between the chronoreceptors and the circadian pacemaker in the brain (Sernagor E 2005).

MINIMIZING JET LAG: A PLAN OF ATTACK FOR RAPID REENTRAINMENT

In 2003, leading British jet lag researchers published a review of clinical trials that used bright light with and without melatonin in an effort to hasten circadian rhythm reentrainment after simulated or actual flights that crossed more than five time zones. They cited 10 randomized, controlled clinical trials that compared the effects of melatonin versus placebo in participants undergoing simulated or actual long-distance travel (Herxheimer A et al 2003) .

Eight out of 10 trials found a clear reduction in jet lag when melatonin was taken. Five of the studies recorded global jet lag scores between zero (none) and 100 (extreme). The mean score after placebo was 48. Mean score after melatonin was 25, indicating that jet lag severity was reduced by about half among melatonin users.

The scientists concluded that 2 to 5 mg of melatonin taken at bedtime after arrival is an effective means of minimizing jet lag (Herxheimer A et al 2003)**.** Melatonin administration at bedtime should probably continue for the following two to four days for maximum effectiveness. In addition, careful attention to meal times and light exposure may hasten reentrainment. Conversely, inappropriate meal times, injudicious use of alcohol or caffeine, and exposure to bright light at the wrong times may hinder the process.

Light was identified as the most important external cue. Specifically, after a westward flight, it is important to stay awake during daylight hours at the new destination and sleep only after it gets dark. After an eastward flight, it is important to remain awake in the morning but to avoid bright morning light. It is also recommended to be outdoors as much as possible in the afternoon at the new destination.

Getting some moderate exercise (Miyazaki T et al 2001) and perhaps indulging in sightseeing at times when bright light exposure is advised may also reinforce the reentrainment process. Doses of melatonin ranging between 0.5 mg and 5 mg are similarly effective in facilitating reentrainment, but one research team found that participants fall asleep more rapidly and sleep somewhat more soundly after 5 mg melatonin than after 0.5 mg. The team also reported that fast-acting rather than timed-release forms of melatonin are more effective for reentrainment purposes (Herxheimer A et al 2001).

It is unclear whether alcohol or caffeine affects adaptation, and the answer may at least partially depend on what an individual is accustomed to. But, these beverages appear more likely to hinder than to help adaptation. It is recommended, therefore, that alcohol and caffeine be used sparingly, at best, until full reentrainment is achieved (Herxheimer A et al 2003).

AN ALTERNATE STRATEGY: PREENTRAINMENT

Preentrainment is another strategy that can be used to help avoid jet lag. Preentrainment is the technique of adjusting to a new time zone before one's departure. Researchers at Rush University Medical Center's Biological Rhythms Research Laboratory in Chicago conducted a study in 2003 using 28 healthy young participants who received one of three protocols, all designed to advance each subject's habitual sleep schedule by one hour per day, for three days, with or without the use of morning bright light. The goal was to arrive at the new destination with circadian rhythms already partially reentrained to local time, thus minimizing jet lag symptoms and facilitating full reentrainment after arrival (Burgess HJ et al 2003).

On each of the three study days, participants were exposed to differing amounts of morning light for the first 3.5 hours after waking. Normal wake time was incrementally advanced one hour each day, simulating the wake time of eastward time zones. Phase shifting (reentrainment of the circadian cycle toward the destination goal) was measured by monitoring changes in melatonin content of the saliva before and after each light session.

As expected, participants who received the greatest amount of bright light on waking experienced the most dramatic phase shift, which equaled about two hours. Even intermittent bright light, which allows a subject enough time to conveniently perform morning chores, such as showering, etc., resulted in a phase shift of nearly two hours with minimal side effects and only a slight reduction in sleep duration (Burgess HJ et al 2003).

The scientific team proposed that its three-day treatment may be especially helpful to eastward travelers, particularly those who travel across multiple time zones and arrive in the morning. They cited previous studies confirming this benefit of early morning bright light exposure, showing that appropriately timed bright light can increase the phase advance more than dim light can (Boivin DB et al 1996; Honma K et al 1995; Miyazaki T et al 2001; Wyatt JK et al 1999; Burgess HJ et al 2003).

In early 2005, the same research team conducted a follow-up study (Eastman CI et al 2005). The goal was again to phase shift participants before an anticipated long-haul eastward flight. As in their previous study, researchers subjected participants to bright light therapy on waking for three days. In this study, however, participants were divided into two groups. One group was awakened two hours earlier than their usual wake time each day; the second group was roused just one hour earlier than usual each day. Both groups were exposed to intermittent bright light therapy for 3.5 hours each morning on waking.

Participants' phase advances were measured by monitoring changes in saliva melatonin content. Participants who altered their wake time by two hours per day experienced a mean phase shift of 1.9 hours. Mean phase shift for the group waking up one hour earlier each day was 1.4 hours. The advantage of advancing the wake schedule by two hours per day was not statistically significant compared with the one-hour-per-day approach. In fact, participants in the two-hour-per-day group eventually experienced misalignment between circadian rhythms and sleep schedules and had difficulty falling asleep. This did not occur among participants in the one-hour-per-day group (Eastman CI et al 2005).

The researchers speculated that a schedule alternating 15 minutes bright light followed by 15 minutes dim light might work as well, or better, than the study's 30 minutes bright/30 minutes dim protocol because it is the initial pulse of bright light that has the greatest effect on entrainment (Eastman CI et al 2005). Finally, the study's authors noted that the recent discovery that the human circadian system is most sensitive to short wavelength (blue) light of about 460 nm might mean that lamps of lesser intensity and with a greater concentration of this blue light may work as well, or better, than a standard, commercially available bright light.

PREENTRAINMENT WITH LIGHT AND MELATONIN

In late 2005, the same research team published the results of a study in which varying doses of supplemental melatonin, administered in the afternoon, were added to participants' bright light exposure on waking (Revell VL et al 2005). Participants received four 30-minute sessions of exposure to bright light from a light box, alternated with 30 minutes of dim room light. This schedule was intended to allow participants the flexibility of completing morning chores conveniently. In the afternoon, participants received either 0.5 mg or 3.0 mg melatonin. Wake time was advanced by one hour each day for three days.

Results were similar to those reported in the 2003 study. Participants phase advancedby about 2.5 hours, with no appreciable jet lag symptoms. Surprisingly, no statistically significant difference was found between participants receiving the smaller or the larger doses of melatonin (Revell VL et al 2005). Thus, morning bright light exposure and an afternoon dose of melatonin of at least 0.5 mg, combined with an incremental advance in wake time of one hour per day for three days prior to travel, may be the most effective approach to preventing, or at least ameliorating, jet lag before flying across more than five time zones.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Jet lag is the bane of modern travelers, but its debilitating effects can be minimized with proper planning. Eastward flight generates far more severe jet lag than westward flight, but the reentrainment procedures outlined here should work for travel in either direction. The following procedure is recommended:

- Attempt to schedule your arrival for morning or early afternoon, if possible.
- Attempt to depart fully rested.
- Expose yourself to (carefully timed) bright daylight.
  - Such light exposure should not commence until two hours before your normal wake time. For example, if you normally rise at 7 a.m., do not expose yourself to light at the destination until the time that corresponds to 5 a.m. at your departure point. Thus on a seven-hour eastward flight, do not expose yourself to light until noon at your destination.
- Take 0.5 to 5.0 mg **melatonin** by mouth within three hours of desired bedtime at the destination.
- Sleep in absolute darkness, to the extent possible.
- Avoid caffeine after noon.

To beat jet lag on a long-distance eastward trip, consider the following preentrainment procedure. This strategy requires that you take action at least three days before departure. While flights across more than five time zones are of greatest concern, preentrainment may be useful for flights that cross as few as two or three time zones. For two-time-zone flights, begin two days before departure.

- For each of the three days before departure, set your alarm for one hour earlier than your usual wake time.
- Immediately on waking each day, expose yourself to bright light.
- For 3.5 hours after waking each morning, including the morning of your departure, alternate 30 minutes of exposure to bright light with 30 minutes of exposure to ordinary room light.
  - Perform morning chores requiring mobility (e.g., showering, shaving, etc.) during bright-light phases.
  - Tasks such as working on a computer, applying makeup, or gardening outdoors without hat or sunglasses may be

completed during bright-light phases, as long as full bright-light exposure is not compromised.

- Take 0.5 to 3.0 mg supplemental **melatonin** in late afternoon (3 to 5 hours before desired bedtime).
- Attempt to retire to bed one hour earlier than usual.
- Attempt to sleep in absolute darkness.
- Repeat procedure, again setting wake time another hour earlier than usual, for two more days. By day three you should be waking three hours earlier than usual.
- Avoid caffeine after noon.

JET LAG SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a "heavy head," or gastrointestinal symptoms such as nausea and diarrhea.

For more information see the Safety Appendix