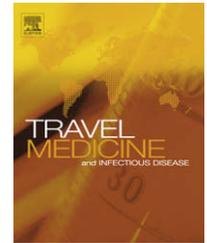




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Some chronobiological and physiological problems associated with long-distance journeys

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Summary Long-distance travel is becoming increasingly common. Whatever the means of transport, any long journey will be associated with “travel fatigue”. The symptoms associated with this phenomenon result from a changed routine (particularly sleep lost and meals) and the general disruption caused by travel. Planning any trip well in advance will minimise many of these problems, but some factors are less easy to guard against. These problems include sitting in cramped and uncomfortable conditions and, with flights, the hypoxic environment in the cabin.

After arrival at the destination in another country, there can be problems coping with the local language, alterations in food and different customs. If the flight has crossed the equator, then there is likely to be a change in season and natural lighting and, if it has crossed several time zones, there will also be the problem of “jet lag”, caused by a transient desynchrony between the “body clock” and the new local time.

Moreover, the new environment might differ from the place of departure with regard to ambient temperature and humidity, altitude, natural lighting (including ultraviolet radiation) and pollution. The traveller needs to be aware of these changes before setting off, so that appropriate preparations (clothing, for example) can be made.

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Introduction

Travel has become part of contemporary lifestyles. Many journeys take a long time whether they are by plane, road

or rail. All such journeys result in “travel fatigue” on the day of travel; journeys which also cross time zones result in “jet lag”, a condition that might take several days to disappear. A further result of travelling, often over quite short distances, is that the new environment differs from that at the starting point. There might be changes in altitude and pollution might be particularly high or low. Changes in climate can often be expected also, and individuals travelling across the equator will experience differences in the season and natural lighting. In addition,

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there are likely to be changed culture and customs, including differences in the food that is eaten, the times when it is ingested, and the way in which it is prepared.

The aims of this article are to outline current views on the nature and origin of the problems, and to offer advice on how to minimise their adverse effects. Travellers can control some of the problems, provided that sufficient and appropriate planning of the trip has taken place as far in advance as possible. These plans should include having all the necessary documents and health checks, discarding personal items that would compromise security measures, and having alternative courses of action in case of travel delays. Appropriate clothing for the new environment is another means whereby many problems can be circumvented by suitable planning before the journey begins.

Travel fatigue

So-called “travel fatigue” is associated with any long journey, regardless of the mode of transport and the number of time zones crossed^{1,2}; its symptoms include disorientation, general weariness and increased incidence of headaches. Travel fatigue is a non-specific response to the many hassles that travel might bring, including disruption of the normal daily routine, spending too much time in cramped and uncomfortable surroundings, and eating different (and often less palatable) food at unaccustomed times during the journey.^{3,4}

Dehydration is an important component of travel fatigue, particularly if the traveller sits in the direct glare of the sun. In flights, dehydration arises also due to exposure to the dry air that is circulated in the cabin during the flight. The problem is exacerbated by the fact that the air on board is not only dry but at a pressure that is lower than that at sea level (corresponding to an altitude of about 3000 m) and hypoxia independently produces subjective symptoms that are similar to travel fatigue. This low level of hypoxia is unlikely to cause difficulties except to individuals with breathing discomfort. Hypoxia has been found to modify the daily secretory profiles of some hormones.^{5,6}

During the days immediately after long-haul flights of 8 h or more, there is an increase in the incidence of pulmonary embolism and deep vein thrombosis (DVT) (see reviews^{7–12}). Episodes are often asymptomatic and up to 10% of travellers might be affected,^{13,14} though clinical treatment is generally not required. When patients who are being treated clinically for pulmonary embolism or DVT are considered, the proportion that has recently undertaken a long-haul flight is higher than in the population in general.^{15,16} The incidence is higher in travellers who also have other risk factors, including: over 45 years of age, a history of thromboembolism, more than three pregnancies and obesity, for example.^{17–19} Immobility, cramped seating conditions, dehydration and hypoxia of the cabin air are generally cited as combining to cause the increased incidence of pulmonary embolism and DVT.

During long-haul flights also, the blood becomes hypercoagulable, fibrinolysis is reduced, and the legs and ankles become oedematous.^{20,21} Similar haematological changes have been observed after long-distance travel by land^{22,23} and remaining in the sitting position produces many

changes in the blood supply to the legs.²⁴ Since many of these last changes are observed at sea level, the role of hypoxia seems relatively unimportant, though it has been suggested that older travellers will be more adversely affected by hypoxia.^{25,26}

Advice on dealing with travel fatigue

Planning the journey well in advance, arriving well before departure time, and having all the necessary documents for travel to the final destination, are all ways of minimising the disruption and problems associated with travel in general.^{1,2,27,28}

Dehydration during the journey can be countered by increasing fluid intake, though diuretics such as caffeine and alcohol, which can accentuate fluid loss, should be avoided and be replaced by fruit juice or water.^{1,2,29,30} Performing exercises as well as maintaining hydration is believed to help avoid pulmonary embolism and DVT,³¹ but space limitations will restrict the type of activity that is feasible, and travellers might be limited to stretching exercises or isometric exercises in their seat.²⁹

For journeys lasting more than about 6 h, particularly if the traveller is at high risk, additional prophylactic measures are suggested. There is some evidence favouring the use of an anti-coagulant such as low molecular weight heparin,³¹ fibrinolytic agents,³² drugs reducing oedema,³³ and knee-length support stockings that prevent pooling of the blood in the lower leg and ankles,^{34–37} though the absence of clear guidelines has been stressed.³⁸

The symptoms of travel fatigue can be remedied on arrival at the final destination. Possibilities include rehydration, a rest or short nap, some light physical activity, and a shower.^{1,2,29} Any nap should be short so that a full sleep can be taken later that night; the nocturnal sleep should present no problems, since time at the destination and place of departure coincide.

With adherence to the above advice, the traveller can expect the symptoms of travel fatigue to have worn off by the next day.

Symptoms of jet lag

A flight across three or more time zones gives rise to “jet lag” in the new time zone.^{1,2} The symptoms of jet lag are included in Table 1 and extend from labile affective states to periodic impairments in decision-making, transient underperformance and digestive discomfort (Table 1).

Table 1 Some of the symptoms associated with travel fatigue

Fatigue during the daytime (coupled with difficulties in sleeping satisfactorily during the night).
Loss of appetite (and indigestion and feeling “bloating” if food is eaten).
Decreased abilities to concentrate and to maintain motivation to perform tasks.
Increased irritability and lability of other mood states.

Based on Refs.^{1,2}

These symptoms are more marked after eastward than westward flights, and are more severe and prolonged the greater the number of time zones crossed. One symptom reliably associated with jet lag is fatigue, but the perceived importance of the other symptoms depends upon the time of assessment. Jet lag in the morning is strongly associated with poorer sleep the night before but, during the daytime, it is associated more with decreased abilities to concentrate and to maintain motivation and increased irritability. In the evening, jet lag is associated with not feeling tired and ready for the next sleep.^{39,40}

The transient desynchrony between the individuals' new environment (the timing of which alters accords with the new time zone) and their "body clock" (which is slow to change its phasing from the old time zone) is the root cause of jet lag. This desynchrony is abnormal, individuals' body clocks normally being in phase with their environment. The symptoms of jet lag regress as the normal synchrony between the body clock and the new environment are re-established. In order to comprehend clearly the implications of this loss of synchrony, it is necessary to understand the properties of the body clock and the influence it exerts upon an individual's physiology.

The body clock

The body clock consists of two suprachiasmatic nuclei (SCN), found at the base of the hypothalamus. "Clock genes" within each cell of the SCN are transcribed and then translated (via mRNA and ribosomes) into "clock proteins". These proteins exert effects throughout the cell and also produce products that move back to the nucleus and inhibit the transcription of clock DNA. The fall in clock mRNA that arises in this way leads to a fall in the concentration of clock proteins and, therefore, a loss of inhibition of DNA transcription. As a result of this, the cycle begins again. Normally, it takes about 24–25 h to complete a single cycle.^{41,42}

The SCN cells not only behave autonomously but also have receptors for melatonin, the hormone released by the pineal gland; the SCN cells also receive light information from the eyes via a direct pathway, the retinohypothalamic tract, and information about physical activity and general "excitement" via the intergeniculate leaflet.⁴³ The body clock is close to areas of the brain that regulate the whole body – via temperature regulation, hormone secretion, the autonomic nervous system, and the sleep–wake and feeding cycles.

When individuals are studied in environments where there are no time cues, in an underground cave, for example, their rhythmic lifestyle continues – confirming that it is produced independently of external rhythms – but it shows a period that is closer to 25 h than to 24 h. It is for this reason that the observed rhythms are called circadian (from the Latin: about a day). This periodicity was originally believed to be a pure reflection of the intrinsic period of the body clock, but this belief is no longer thought to be the case. It is now believed that the period measured under these circumstances is influenced by the light–dark cycle (see later) and that the true period can only be estimated by protocols which use very dim light (<10 lux) during the wake time, or protocols that use blind subjects. In these

circumstances, the period of the clock has been found to be about 24.3 h, and this is considered to be a more accurate reflection of its intrinsic value.⁴⁴

Adjusting the body clock

Irrespective of the exact value for the intrinsic period on the body clock, for it to be of value, it and the rhythms it drives need to be synchronized to a solar or tidal day. This adjustment is achieved by zeitgebers (German for time giver), the term given to rhythms resulting from the animal's environment. Zeitgebers adjust or "entrain" the body clock to the period of the zeitgeber. In different animals, rhythms of the light–dark cycle, food availability–unavailability, physical and mental activity–inactivity, being buffeted and inundated by the tides, and social influences have been found to act, singly or in combination, as zeitgebers. For most land-dwelling creatures, the body clock is entrained to the solar day (24.0 h), but in shore-dwelling creatures, it is adjusted to a period of 24.8 h, equal to that of the tides. In humans, who are adjusted to the solar day, the most important zeitgebers are the rhythms of the light–dark cycle and melatonin secretion; other zeitgebers appear to play minor roles only.

The effects of light acting upon the body clock in humans depend on the time of presentation relative to the time of the temperature minimum (normally around 04:00–05:00 h). Light exposure in the 6 h after the temperature minimum advances the body clock, in the 6 h before the minimum, it delays it, and at other times exerts no effect upon the body clock.⁴⁵ This non-parametric relationship between the time of light exposure and the phase shift of the body clock that it produces is called a Phase Response Curve (PRC). The size of the phase shifts produced depends upon the intensity of the light, domestic lighting being much weaker than natural light and so exerting a smaller effect.⁴⁶ Many individuals have very limited exposure to natural daylight outdoors, but natural light passing through windows and domestic lighting (which, due to our normal routines, combine to produce a rhythm which has a period of 24 h) are sufficient to entrain the circadian clock to a 24-h rhythm.

The pineal hormone, melatonin, also acts as an important zeitgeber in humans. Its secretion is normally highest during nocturnal darkness and negligible during diurnal light, the onset of secretion being at about 21:00 h in the evening. The secretion of melatonin is controlled by the body clock via the sympathetic nervous system. Both endogenous (that secreted by the pineal gland) and exogenous (that ingested) melatonin produce a sense of sleepiness, and ingested (and, it is presumed, endogenous) melatonin also adjusts the phase of the body clock via the melatonin receptors found on the SCN cells (see above). The shifts produced tend to be the inverse of those produced by light,⁴⁷ ingestion in the afternoon and early evening advancing the body clock and, in the night and early morning, delaying it.

It is obvious from the above that there is an interaction between the SCN and the pineal gland, and this is made more complex by the fact that light inhibits melatonin secretion. The result of this interaction is that the clock-shifting effects of these two zeitgebers normally reinforce each other. Bright light in the first hours after the

temperature minimum advances the body clock, not only directly (via the PRC to light) but also indirectly (by suppressing melatonin secretion and so preventing the phase-delaying effect that melatonin would have exerted at this time); bright light in the evening and early part of the night (before the temperature minimum) will also exert direct and indirect effects upon the body clock, but in the opposite direction.

Roles of the body clock

The body clock exerts two general influences upon the body's physiology. First, it promotes daytime activities (physical and mental activity and the metabolism of glucose) and separates them from nocturnal inactivity (when consolidated sleep rather than activity is required, fat is preferentially metabolised, and hormonally mediated recovery and restitution occur). Second it prepares individuals in the evening for going to sleep and then prepares them in the second part of sleep for waking up in the morning. These changes require an ordered sequence of biochemical and physiological events.

To understand more fully the causes of jet lag, more detailed explanations of the normal effects of the body clock upon rhythms of core temperature, sleep, and physical and mental performance are required.

Body temperature rhythm

In subjects living normally (asleep at night and active in the daytime), core temperature shows higher values in the daytime and lower values at night (Fig. 1).

These results might indicate that the body is responding to a day-active society, with sleep and recuperation taking place at night. Such an explanation is only partially correct, as is indicated by a "constant routine" protocol. In this protocol, subjects are required to behave as follows: to stay awake and sedentary for at least 24 h in an environment of constant temperature, humidity, and lighting; to

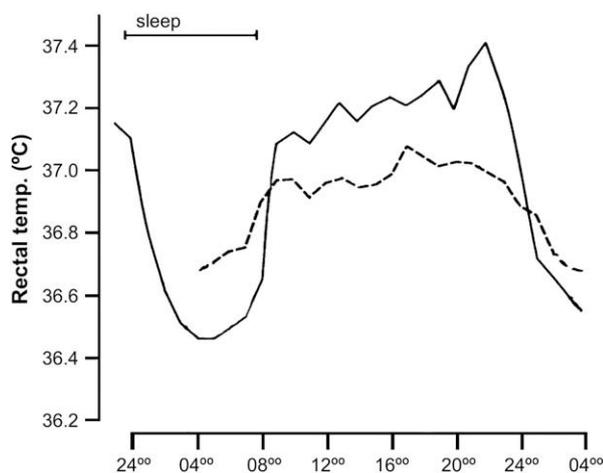


Figure 1 Mean circadian changes in core (rectal) temperature measured hourly in eight subjects: living normally and sleeping from 24:00 to 08:00 h (solid line); and then woken at 04:00 h and spending the next 24 h on a "constant routine" (dashed line). (Based on Ref. ⁴⁸)

maintain the same posture and engage in similar activities throughout this interval, generally reading or listening to music; and to eat identical meals at regularly spaced intervals. With such a protocol, any rhythmicity due to the environment and lifestyle has been removed. However, as indicated in Fig. 1, the rhythm of core temperature (and other variables that have been studied) persists, even though its amplitude is decreased. Three general deductions can be made from these findings:

1. The rhythm observed during the constant routine must be endogenous and arise within the body; its generation is attributed to the body clock.
2. Effects due to the environment and lifestyle are normally present, since the two rhythms not identical; this difference is termed the "exogenous" component of the rhythm and, in the case of body temperature, it consists of increases caused by light and different types of activity (mental, physical, social, and so on) during waking, and decreases caused by darkness, a change in posture, sleep and inactivity during the night.
3. In subjects living a conventional lifestyle, these two components are in phase. During the daytime, the body temperature is raised by the body clock acting in synchrony with the environment and activity; during the night, the clock, environment and inactivity all synchronously reduce core temperature.

Sleep rhythms

Conditions propitious for sleep – a quiet, dark and comfortable environment – are easily produced in sleep laboratories and have enabled circadian rhythms in sleep propensity (the ease of initiating sleep), sleep maintenance and waking from sleep to be investigated.^{49–51} The ability to get to sleep is inversely related to core temperature so that, in subjects living normally, sleep onset is quicker during the night (when core temperature is lower) and more difficult during the daytime (when core temperature is higher). Moreover, the chance of waking spontaneously from sleep is low when core temperature is near its trough and rises markedly after this trough. Conversely, the chance of waking up during the daytime is high (even supposing that the individual is asleep at this time), because core temperature is high, but this chance rapidly diminishes in the evening as core temperature begins to fall.

Combining these results enables the effects of core temperature upon sleep length to be considered. Sleep might be easy to initiate in the middle of the night, but it will be curtailed by the morning rise of core temperature. Conversely, even though sleep is difficult to initiate in the early evening (because core temperature is too high), if sleep is actually achieved, then it might be quite long-lasting, since waking is not likely to occur until after the temperature trough. In practice, going to bed in the evening, when the core temperature is beginning to fall, will usually enable an individual to gain the normal 6–8 h of uninterrupted sleep before the rise in core temperature the following morning.⁵² The evening fall of core temperature is closely associated with the onset of melatonin secretion (about 21:00 h), and links between increasing sleep

propensity, declining core temperature and rising melatonin secretion have been stressed.^{50,51,53,54}

Physical and mental performance rhythms

Aspects of physical performance, such as self-chosen work-rate and peak force produced by various muscle groups (for review, see Ref. [1]), show circadian rhythms that are in phase with core body temperature or adrenaline (which peaks slightly earlier in the daytime). Recent work⁵⁵ using a 3-h ultra-short sleep-wake cycle protocol, a variant of the "constant routine", has confirmed the similar phases of these rhythms. The synchrony with core temperature is seen also when physiological processes that are closely associated with exercise (heart rate, ventilation and blood lactate, for example), and performance in several athletic skills in simulated contests or time-trials, are considered.^{56,57} A causal link between these rhythms has often been suggested but this link has not been tested in any intervention studies.

Sleep loss produces comparatively minor effects upon physical performance per se. Nevertheless, sleep loss will affect physical performance indirectly through a declining motivation, decreased desire (or ability) to perform accurately a task that requires fine motor control, and a compromised ability to make decisions regarding strategy, for example (see below).^{1,58-60}

Rhythms in mental performance and mood tend to be phased similarly to that of core temperature, and similar causal links have been proposed.^{58,61} Important differences are discernible between the circadian rhythms of physical and mental performance when their detailed timing is investigated. Mental performance rhythms differ from each other due to the different rates of decrement that occur with increasing time spent awake. This decremental trend is generally described as "fatigue", and can be considered to be the exogenous component of the rhythm. As a general rule, mood and complex mental performance tasks (mental arithmetic and multi-tasking, for example) show a greater rate of deterioration due to time awake than do simpler mental performance tasks. Consequently, simpler mental tasks parallel physical performance and core temperature more closely than do complex tasks, which peak earlier in the day (Fig. 2). A further important difference between mental and physical performance is that prior sleep loss causes poorer mental performance. This susceptibility of mental performance tasks to sleep loss can lead to inattention, an increased incidence of errors and even accidents.⁶³

In summary, the body normally shows a multitude of circadian rhythms that reflect the fact that humans are rhythmic creatures living in a rhythmic environment. These circadian rhythms are produced not only by the body clock (the endogenous component) but also by direct effects of the individual's environment and lifestyle (the exogenous component). Under normal circumstances, these two components are, due to the action of the zeitgebers, synchronized to each other (see Fig. 1, full line). The result of this synchronization is that, in the daytime, the body is in an "active" mode and, during the night, the opposite conditions hold and the individual can sleep and recuperate.

A further key property of the body clock is that it is robust, little affected by transient changes such as a daytime nap or a brief nocturnal awakening. Such stability is common

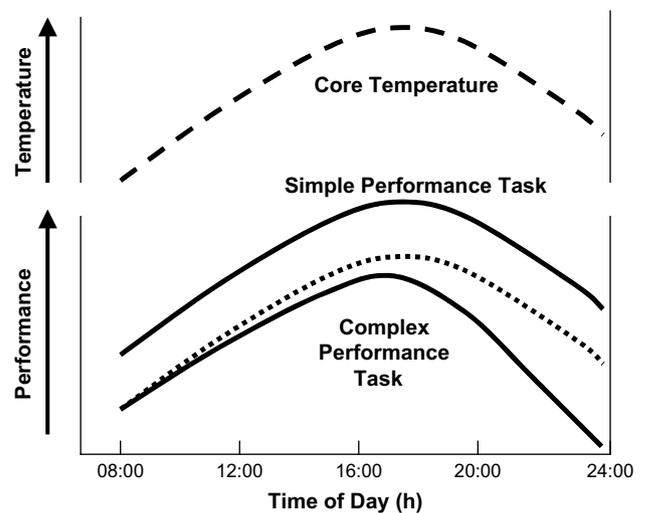


Figure 2 Illustration of the diurnal rhythms of, top, core temperature (dashed line) and, bottom, simple and complex performance tasks (full lines). The dotted line shows the time-course of a complex performance test (parallel to the rhythm of core temperature) that would occur in the absence of effects due to fatigue. (Based on Ref. ⁶²)

to the circadian rhythms of all animals so far studied, and seems to have provided an ecological advantage during evolution. However, it can become disadvantageous to humans in some circumstances, our social evolution having outstripped our biological evolution.

Jet lag and the body clock

Due to its robust nature, the body clock (the endogenous component of a circadian rhythm) does not adjust its phase to the new time zone for some days after arrival, even though the environment itself (the exogenous component) changes immediately. In other words, an abnormal mismatching, or desynchrony, between the endogenous and exogenous components of the circadian rhythms occurs. It is this loss of the normal synchrony between the endogenous and exogenous components of a rhythm that causes the symptoms of jet lag. Travellers might be trying to integrate their lifestyle into the new environment, but this will no longer accord with the physiological and biochemical rhythms being promoted by the body clock. Sleep may be used as an example: after a westward flight across eight time zones, the individual will feel tired at 16:00 h local time (equivalent to 24:00 h in the time zone just left, the time zone to which the body clock is still adjusted), and will then begin to feel more alert at local midnight (corresponding to 08:00 h on "body time"); by contrast, after an eastward flight across eight time zones, the individual does not feel tired at midnight by local time (16:00 h on body time), but is ready to go to sleep as the new day dawns at 08:00 h (24:00 h by body time).

Physical and mental performance, and the body's appetite for food, are all affected to some extent and for the same reasons. Possible problems with food intake will be dealt with in a later section but at this point it is sufficient to realise that the appetite for food, the ability of the gut to digest it and absorb its products, and the

abilities to metabolise and store absorbed food products will all be compromised.⁶⁴ Athletes at all levels of achievement show altered performance in the days after time-zone transitions,⁶⁵ because aspects of physical performance retain a parallelism with body temperature and the body clock and so are inappropriately timed for the destination. Any decrement will be most marked if a sports event is held at a time corresponding to the night in the time zone just left. Mental performance and mood also deteriorate.⁵⁸ Again, this deterioration is partly due to the inappropriate timing of the body's temperature rhythm but there is the additional problem that mental performance is worse after sleep loss (and this will occur due to the unadjusted temperature rhythm, see above). After a time-zone transition, there is likely to be the possibility of a "double negative" (performance after sleep loss *and* too near to the trough of the temperature rhythm), and this combination can cause a substantial decrement in mental ability.

Inter-individual differences and flight direction

The amount of jet lag experienced differs between individuals, but there has been little success so far in predicting those who will be most affected (for summary of the position, see Ref. [2]). It has been argued that jet lag will be less marked in younger subjects, in physically fitter subjects, and in subjects with flexible sleeping habits. It has also been argued that "larks" or "morning types" (who like to go to sleep and get up early and to perform important tasks in the first part of the waking day) will suffer less after flights to the east than will "owls" (who like to go to sleep and get up late and to perform important tasks in the latter part of the waking day). It has been suggested that this difference is because larks are better able to deal with the earlier times of retiring and rising required by an eastward flight. There is a complementary prediction – that larks will suffer more than owls after flights to the west, since they are less well able to cope with the delayed times of retiring and rising required in this circumstance. The evidence in favour of any of the above predictions is unconvincing.

By contrast, one study⁶⁶ embraced a group of elite athletes and ancillary staff travelling 10 time zones to the east from the UK. Jet lag was less in those who had undertaken the journey before and in whom, due to the flight arrangements, the interval between their last, full nocturnal sleep in the UK and their first, full nocturnal sleep at their destination was less. This difference was observed in spite of the fact that those suffering less jet lag had slept less during the flight itself.

In summary, there is little evidence that personal characteristics play an important role in determining the severity of jet lag suffered by individuals; it seems that appropriate planning of the trip has a greater impact. By contrast, flights to the west (requiring a delay of the body clock) are generally associated with less jet lag.^{2,67} Reasons for this include: (1) it is easier to get to sleep following a delay than an advance in bedtime because the ease of getting to sleep, *ceteris paribus*, increases with the amount of fatigue and prior waking time; (2) the body clock tends to run with a period slightly in excess of 24 h (see above), so delaying it is intrinsically easier than attempting to advance it; and (3) the effect of exposure to the natural light–

dark cycle at the destination naturally promotes the appropriate adjustment of the body clock (see below).

Advice on dealing with jet lag – general principles

Since the body clock is slow to change its phase, for sojourns of only a few days in the new time zone before returning home, adjustment is not possible. In these cases, travellers are advised to time appointments in the new time zone to coincide with daytime in the home time zone that has been left, and to avoid times that coincide with night on "body time".⁶⁸ After a flight to the east, therefore, the new afternoon is preferable to the new morning (coincident with morning and night, respectively, on home time); after westward flights, the new morning is preferable to the late afternoon and evening (coincident with afternoon and night, respectively, on home time).

When stays in the new time zone last more than a few days, adjustment of the body clock is possible. Since subjective symptoms of jet lag disappear, and objective measurements of poorer sleep and performance improve, as the body clock adjusts to the new time zone, there is an obvious premium on promoting such adjustment. Even following the advice given below, individuals will find that adjustment takes about one day per time zone crossed after an eastward transition, and slightly less after westward transitions. Accordingly, to enable this adjustment to occur, any trip should be planned so that arrival takes place a number of days before an important engagement.

Adjustment can be achieved pharmacologically or behaviourally. The "pharmacological" approach requires the use of "chronobiotics", substances that can alter the phase of the body clock⁶⁹; the "behavioural" approach requires appropriate timing of zeitgebers in the new time zone. The pharmacological approach can also be used to ameliorate the symptoms of jet lag, even if the body clock is not being adjusted by the treatment, in much the same way that a pain killer can alleviate a headache without targeting its cause.

Advice on dealing with jet lag – before and during a flight

Whether or not adjustment of the body clock is feasible (see above), there are some courses of action that can be taken before and during the flight. Pre-flight factors include planning the journey so that the stress and hassles of the flight and reaching the final destination are minimised, already covered in the section on Travel Fatigue. If adjustment of the body clock is being aimed for, it might be possible also to make minor changes to the sleep–wake cycle in the days before the flight, retiring and rising earlier than usual before a flight to the east, and later than usual before one to the west.⁷⁰ However, changes of sleep times more than 2 h are inconvenient and are likely to be counter-productive, causing the kind of problems associated with working nocturnal shifts.

Upon entering the aircraft, travellers could set their watches to destination time, and use these times to decide whether or not to take a nap, the best time for a nap being when it is night in the destination time zone. However, sleepiness will be greatest when it is night in the time zone just left, and napping at this time will hinder adjustment to the destination time zone. In such cases, attempts to stay

awake should be made, by strolling round the cabin or making use of the in-flight entertainment system.

Few systematic studies seem to have been made of the value of melatonin or hypnotic drugs (barbiturates and benzodiazepines, for example) in promoting sleep in this environment. Recent reviews have advised against their use, particularly in aircrew,⁷¹ and Richardson et al.⁷² pointed out the need for practical guidelines.

It would be ideal if the type of meal eaten and the time of eating it were appropriate for destination time but, in practice, meals are determined by the carrier and generally consist of full meals soon after take-off and just before landing. In the past, the traveller has had no control over the timing of in-flight meals, but it is now becoming possible in some cases to ask for meals at times suited to the traveller. Appetite is lessened during long-haul flights, particularly later in the flight.⁴ This decrease in enjoyment of food might reflect some combination of effects due to cabin hypoxia, the limited types of food available, the manner of preparation of the food, and having been woken from sleep. Travellers are also reminded of advice, given in the section on Travel Fatigue, regarding the maintenance of hydration levels and taking bouts of exercise.

Advice on dealing with jet lag – pharmacological approaches after a flight

Promoting alertness

Several drugs, including amphetamines, pemoline and modafinil, have been shown to increase alertness after waking and sustain performance during extended periods without sleep.^{73–75} These drugs have often been tested in a military context and, even then, their value is controversial. Apart from promoting wakefulness, these drugs have several disadvantages: (1) their use can be counter-productive since they also reduce the ability to initiate and sustain sleep; (2) extended use can lead to drug dependence; and (3) their effects on mood and mental performance have not been investigated in sufficient detail to merit unequivocal support. They are also to be found on the list of banned substances for athletes. These drugs are unacceptable for use by civilian aircrew and normal travellers, therefore.

By contrast, caffeine is widely used. At a dose equivalent to about two cups of coffee, it has been shown to produce a temporary improvement in alertness during a night without sleep.^{76,77} In a recent study,⁷⁸ the effect of caffeine (100 mg 3 h before sleep followed by 100 mg 1 h before sleep) upon nocturnal sleep and a daytime recovery sleep following one night of total sleep deprivation was investigated. Caffeine increased sleep latency and decreased the amount of Stage 2 and SWS (slow wave sleep), but the effects were more marked in the daytime when, in addition, total sleep time and REM (rapid eye movement) sleep were decreased. This study might be particularly relevant since nocturnal sleep in the new time zone might coincide with “daytime” by body time.

Currently, the best advice would seem to be that drinking coffee at the new breakfast time is appropriate. In contrast, it is contraindicated in the evening.

Promoting refreshing sleep

Soporific drugs or short-acting hypnotics can be useful, assuming that a real need for them exists. Amongst these

drugs are the benzodiazepines (or minor tranquillisers, for example, temazepam) and drugs acting on benzodiazepine receptors (for example, zolpidem).^{79–82} Taken in the evening before retiring, they effectively promote sleep⁸³ and, if short-acting, they do not cause sleepiness the next day. However, it has not always been established what effect these drugs have upon mental and physical performance after waking from the drug-induced sleep. Moreover, in those cases where improved alertness, physical performance and decreased jet lag have been found, whether this improvement reflects better sleep and/or more adjustment of the body clock is unclear.^{80,81}

No benefit resulted from taking temazepam in a study upon athletes travelling five time zones to the west, probably because arriving at destination in the late evening by local time helped the subjects to sleep without the need for any drug assistance.⁷⁹ Some benzodiazepines seem to affect short-term memory, but this improvement does not apply to zolpidem (zopiclone) and zaleplan, which also have shorter half-lives than temazepam. Even so, Daurat et al.⁸¹ found no effect of zopiclone (7.5 mg) on jet-lag scores after a flight across five time zones to the west. Benzodiazepines with a longer half-life (for example, diazepam and loprazolam) would be unsuitable, due to residual effects on alertness and psychomotor performance the next day; for example, in one study, residual effects of loprazolam on a range of physical performance tasks were found 10 h after administration.⁸⁴

It is clear that further work is required to ascertain which of these drugs, if any, might be of benefit to the traveller in promoting sleep but without compromising performance the following day. It is generally accepted that resorting to the use of sleeping pills should be unnecessary,⁸⁵ except for special cases and under medical supervision. In addition, the reservations expressed by Lemmer⁷¹ and Richardson et al.,⁷² see above, apply also to the present context.

Reviews on the use of melatonin and, more recently, its synthetic agonists and antagonists to treat sleep problems, including those following time-zone transitions, continue to appear regularly – see, for example, recent articles.^{2,86–91} The general view is that melatonin (in doses up to about 3 mg) acts as a natural soporific and produces no hangover effects on performance the following morning.^{92–94} It has, further, frequently been shown to reduce assessments of jet lag after real or simulated flights, and to improve sleep in the laboratory (reviewed in Ref. [95]). All these results attest to its potential value, but no long-term toxicological data are currently available.⁹⁶ Without a licence, there is no obligation for undesirable side effects following melatonin use to be recorded. The purity of melatonin bought via the Internet cannot be guaranteed. For these reasons, melatonin cannot be recommended unless the individual has taken medical advice.

Evidence failing to support the value of melatonin in dealing effectively with a variety of sleep problems, including sleep restriction after time-zone transitions, has come from the meta-analysis of Buscemi et al.⁸⁷ The authors concluded that: “there is no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder”. However, they also concluded

that there was evidence that melatonin was safe with short-term use up to a period of three months.

The chronobiotic function of melatonin (that is, whether or not it adjusts the body clock) is less clear. The demonstration of a PRC for melatonin⁴⁷ means that the timing of ingestion is critical, according to whether a phase advance or delay of the body clock is sought. Taken prior to the trough in body temperature, melatonin promotes a phase advance; taken afterwards, it causes a phase delay (considered above). Accordingly, the required time of ingestion to promote the desired phase shift can be inconvenient after certain time-zone transitions (if required during the night), and also counterproductive after others (if required during the daytime) due to the soporific effect that occurs whenever it is taken (see Ref. [97], for example). Currently, there are no data indicating whether or not melatonin promotes adjustment of the body clock in the required direction under field circumstances, where phase shifts due to the light–dark cycle might over-ride those due to the ingested melatonin.

The possibility that drugs might be used to adjust the body clock has been considered,⁶⁹ but such chronobiotics remain to be found and tested fully. It has been claimed that zopiclone promotes readjustment of the rest-activity rhythm and helps restore the phase relationship between the sleep and temperature rhythm,⁸¹ but much more research work on this area is required.

Advice on dealing with jet lag – behavioural approaches after a flight

Light at all times promotes mental activity, and the colour of the light can influence an individual's mood.⁹⁸ It is the PRC to light⁴⁵ that becomes the basis of promoting adjustment of the body clock. Few field studies that have specifically addressed the shifts of the body clock produced by such treatments.⁹⁹ In one study,¹⁰⁰ the symptoms of jet lag (measured on the Columbia jet lag scale, see Ref. [101]) were compared in a small sample of aircrew with their pattern of exposure to bright light at their destination. Analysis of the results suggested that light exposure produced a small, but statistically non-significant, fall in the amount of jet lag. It would be valuable to repeat this kind of study with a larger sample of subjects, but it might also be necessary to have much stricter control over light avoidance as well as exposure (see below).

Based on the known properties of the PRC to light,⁴⁵ the use of the bright light (and its avoidance) depends critically upon the number and direction of time zones that are crossed, as will now be considered in detail.

Eastward flights across up to eight time zones

After an eastward flight across up to eight time zones, the body clock needs to be advanced. Light exposure in the 6 h after the core temperature minimum and, equally important, an avoidance of light in the 6 h before the temperature minimum (which would shift the body clock in the wrong direction) are required to do so. For both times of light exposure and avoidance, these “body” times must be converted to the new local time. Fig. 3 shows this conversion as it applies to the first day in the new time zone. In devising Fig. 3, it was assumed that the individual's mid-sleep is normally at 04:00 h; if mid-sleep is earlier or

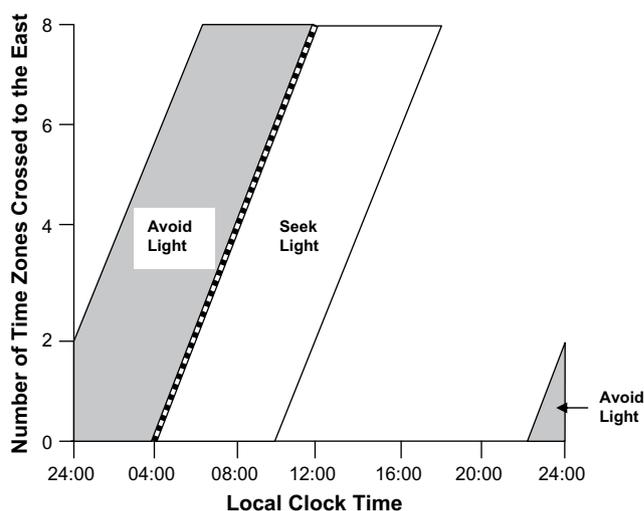


Figure 3 Times of light avoidance and exposure on the first day after EASTWARD time-zone transitions. Dashed line indicates temperature minimum. (Based on Ref. ¹⁰²)

later than this time-point, then all the times shown in the figure will have to be adjusted accordingly.

As an illustration of the use of Fig. 3, consider an eastward flight over eight time zones (from Los Angeles to London or London to Beijing, for example). Light has to be avoided between 06:00 and 12:00 h and sought from 12:00 to 18:00 h by local time. If the individual's time of mid-sleep is 03:00 h, then these intervals become 05:00–11:00 h and 11:00–17:00 h, respectively. On subsequent days, the local times of light avoidance and exposure need to be advanced by 1–2 h each day until light avoidance coincides with nocturnal sleep.

It will be noted that morning light after waking should be avoided for the first few days. In practice, this requirement can be difficult to achieve, particularly on the day of arrival, since many flights are overnight and land in the morning, the traveller having marvelled at a fine sunrise whilst coming in to land! The only solution is to wear sunglasses that are as dark as possible (provided that they do not jeopardise safety when walking), and to try and reach the dimmer indoor light of the final destination and stay indoors and away from the windows as soon as possible.

Eastward flights across more than eight time zones and all westward flights

For flights through more than eight time zones to the east, and for all westward flights, the aim is to promote a delay of the body clock. This aim means that an eastward flight across, for example, 10 time zones is to be treated as a westward flight, requiring a delay of the body clock, across 14 time zones. (The direction in which the journey actually takes place is immaterial; it is the difference between the home and destination time zones that is the relevant factor.) To delay the body clock requires exposure to light in the 6 h before the temperature minimum and avoidance of light in the 6 h afterwards. Once again, body time has to be converted into local time, and this has been done for the first day after arrival in Fig. 4. Again, as above, the times shown

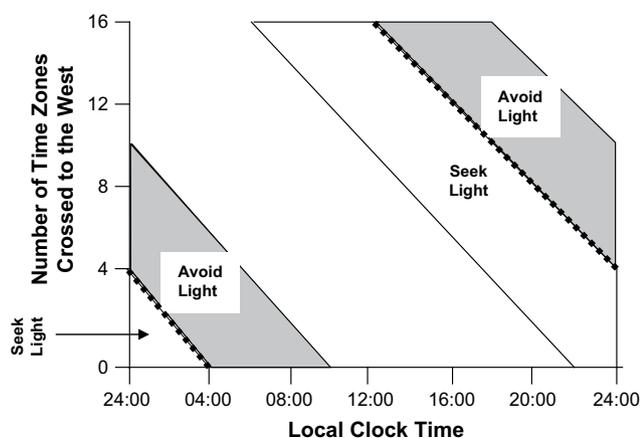


Figure 4 Times of light avoidance and exposure on the first day after WESTWARD time-zone transitions. Dashed line indicates temperature minimum. (Based on Ref. ¹⁰²)

are for a traveller whose time of mid-sleep is 04:00 h, and adjustments for other times of mid-sleep are required. On subsequent days, the local times of light avoidance can, if necessary, be delayed 2 h each day until they coincide with the local night.

The fact that eastward flights crossing more than eight time zones should be treated as ones to the west, and so require the body clock to be delayed rather than advanced, reflects the fact that the body clock tends to run slow (its natural period is in excess of 24 h), and so large delays are more easily to accomplish than are large advances. Phase-delaying the body clock after such journeys has the added advantage that the time of feeling most tired and performing worst delays towards the evening, and so intrudes comparatively little upon daytime activities. For example, after a flight to the east across 10 time zones, greatest fatigue and worst performance are initially at about 14:00 h local time, equivalent to 04:00 h by body time. Delaying the body clock makes these times soon pass outside the most active part of the daytime; by contrast, if the body clock were to be advanced, the times of feeling most tired and performing worst would advance from 14:00 h through the morning, and so intrude more upon normal daytime activities.

It will also be noted that, after a flight to the west, living in synchrony with the indigenous population, and so being in contact with the natural light–dark cycle, tends to result in light exposure and avoidance that are close to the times recommended in Fig. 4. After a flight to the east, by contrast, such “natural” behaviour results in light exposure at the wrong time (see Fig. 3). For example, after a flight from the UK to Los Angeles (eight time zones to the west), light is initially required at 14:00–20:00 h local time, and should be avoided between 20:00 and 02:00 h local time; this requirement accords easily with the natural light–dark cycle in Los Angeles. By contrast, after a flight from the UK to Beijing (eight time zones to the east), light is required at 12:00–18:00 h on local time, and should be avoided between 06:00 and 12:00 h local time; the traveller to the east who tries to promote adjustment by “getting out and about” at the first opportunity is likely to cause the body clock to delay rather than to advance.

It has been suggested that the timing and composition of meals, and taking exercise at appropriate times, can both act to adjust the body clock by acting as a zeitgeber. The evidence that either of these factors could, by itself, promote a sufficient adjustment of the body clock is unconvincing ^{103,104}; moreover, the feeding regime and amount of exercise required would be unacceptable to most travellers. Nevertheless, exercise and mealtimes might play some role as part of “package deals” that attempt to promote adjustment by combining the use of melatonin and zeitgeber exposure.

Combined approaches

Combining light exposure and avoidance with melatonin ingestion, incorporating also exercise regimes and mealtimes and other social zeitgebers, would seem an attractive proposition, as has been suggested by others (see Refs. [105–109], for recent examples). For example, advice exists on times of melatonin ingestion combined with times of light exposure/avoidance for flights to the east or west across different numbers of time zones. ¹¹⁰

In many cases, these suggestions have not been backed up by experimental evidence. However, some laboratory investigations of the combined effects of light and melatonin in promoting phase shifts have been performed. ^{109,111} In one of these, Revell et al. ¹⁰⁹ showed that the body clock could be advanced more (up to 1 h per day) by the combination of early morning light and afternoon melatonin rather than early morning light and placebo. Further, a field study ¹⁰⁶ used a combination of melatonin (3 mg ingested in the evening), light and exercise in athletes travelling across 12 time zones. The athletes were exposed to the natural light–dark cycle when they undertook training sessions in the morning and evening in the new time zone, otherwise remaining indoors. The sleep–wake cycle inverted 2–3 days after the flight and most sleep parameters were unchanged from baseline values. Interpretation of these observations is difficult due to the apparent lack of a control group. Moreover, such research designs mean that it is unknown if the factors acted to promote adjustment of the body clock and/or acted to overcome the symptoms of jet lag (light and exercise increasing daytime alertness and melatonin promoting nocturnal sleep).

In practice, exercise might have a role in addition to any direct phase-shifting effects. Thus, it can be used as an adjunct to light exposure (for example, exercise outdoors with friends) and to light avoidance (meeting friends indoors to relax and chat). Similarly, mealtimes can be used to underpin the regimen in the new environment.

Advice regarding long-distance journeys and dealing with the problems of jet lag is summarised in Fig. 5. It incorporates a series of checks so that decisions can be made within a number of alternatives.

Food intake when the destination is reached

The normal rhythm in eating behaviour is little affected by the body clock (and so effects associated with jet lag are likely to be small and transient) but appetite and the palatability of food are sometimes suppressed by long-distance flights. The small endogenous component of

appetite means that adopting local times for meals after arrival is usually advocated.¹¹² In addition, daily energy expenditure might be reduced for a few days after arrival, due to daytime tiredness.⁶⁶ Bowel movements are often irregular with a stool consistency that is harder or looser than normal. Such changes rarely last for more than a day or so.

Travellers on activity holidays need to have energy intakes that help to sustain their physical activity over their events, whether these are a series of treks, or training manoeuvres. Many athletes benefit from the availability of "sports drinks" when travelling. Portable drinks bottles enable them to ingest fluids regularly, and their carbohydrate and electrolyte contents are valuable additions to the diet. Drinks containing sodium help to promote fluid retention; fluid replacement is important in restoring water balance affected by sweat losses or vomiting. Guidelines for optimal nutrition of athletes who are travelling, at training camps, or en route for competition, have been outlined by Reilly et al.¹¹² Advice was dependent upon locally available food choices, the extent to which personal provisions may be employed, and the means of preparing food for consumption.

Maintaining food hygiene standards is key to avoiding gastrointestinal disturbances when travelling abroad. A majority of travellers are affected by so-called "travellers diarrhoea", the causes of which have been discussed elsewhere.¹¹² Indeed, many of the visiting teams at the 2007 World Cross-Country championships in Kenya, experienced "travellers' diarrhoea", compounded by the high

ambient air temperatures. This disorder is defined as passage of more than three unformed stools in 24 h with discomfort, occurring in a person visiting another country where food contamination may occur.¹¹³ Poor sanitary conditions and poor personal and food hygiene practices are responsible, because ingesting contaminated food or water is the most common cause, the contamination coming from bacteria, viruses or protozoan pathogens transmitted in food or water, or from other people. Symptoms, though severe, are transient and self-limiting.

Sensible eating and drinking habits offer the best means of avoiding "travellers' diarrhoea". The allure of local exotic cuisine must be eschewed where digestive safety is at risk and simple rules may be sufficient to ensure that gastrointestinal problems are not encountered. Prophylactic antibiotics in advance of travelling are not recommended. The use of probiotics in a preventive role has been advocated and may hold promise for the future.¹¹⁴

Environmental challenges at destination

Additional stressors

The environment at destination is unlikely to be the same as that of the home country from which the traveller has departed. Indeed the objective of the journey may be to seek out a different climate for warm-weather activities, participation in winter sports, visiting mountainous regions,

1. For ANY journey that will take a long time, consider the advice on Travel Fatigue (Section 2)
2. Then consider the following tree:

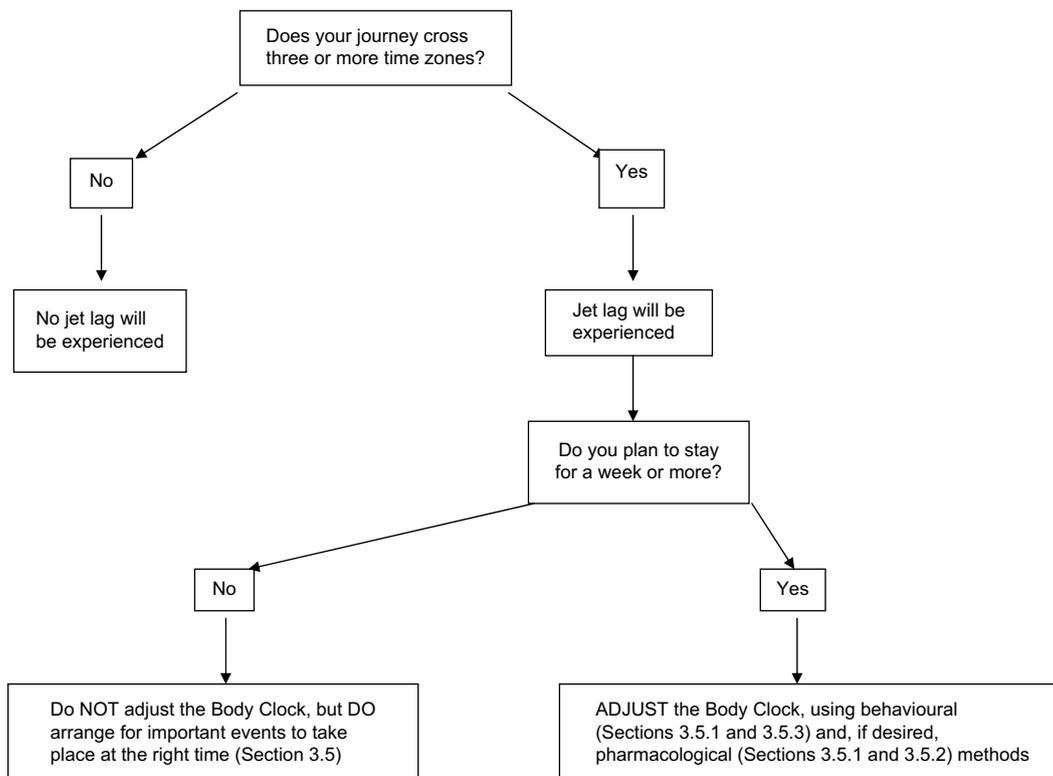


Figure 5 Summary of advice relating to the problems associated with long journeys. (Based on Ref.¹⁰²)

or a variety of other reasons. The journey may be to another hemisphere, in which case an abrupt change of season will be encountered. Alternatively, the air at the city of destination may be polluted. The problems experienced may be in addition to those due to jet lag. Whilst the combination of these factors has not been studied together, their independent effects have been comprehensively investigated (see Ref. [115]).

The growth of the leisure-holiday industry has meant that travellers seek out environmental stress as a part of their holiday-making experience. Alongside this trend is the increasing use of training camps for athletes to secure the physiological benefits associated with acclimatisation. Such adaptations include haematological changes with sojourns at altitude and cardiovascular adjustments due to warm-weather training. Whilst no significant physiological adaptations accrue from cold exposure, protection against hypothermia is essential and may be secured by wearing appropriate clothing and adopting suitable behavioural patterns.

Temperature

Effects of jet lag are compounded in the heat, since any dehydration resulting from the flight will be accentuated by sweating in the hot environment. Visitors should reduce their levels of activity for the first few days whilst adjusting to the hot environment.¹¹⁶ Sunburn may also be a problem and use of a strong sunscreen for protection of exposed skin is advised. After acclimatisation, individuals are better able to deal with heat stress insofar as they can sweat more readily and, due to the actions of the hormone aldosterone, the salt content of the sweat is decreased, so reducing the negative electrolyte balance that would otherwise occur. Individuals with raised blood pressure, or who are overweight, are more liable to suffer in the heat, and so should be particularly aware of the symptoms heat injury.

Individuals may protect themselves against the cold by donning appropriate clothing, and considerable industrial effort has been placed on the ergonomic design of cold-protective garments for such circumstances.¹¹⁷ Attention to weather forecasts before travelling and packing clothing for the worst scenarios predicted are sensible measures that should be undertaken. Hypothermia can occur relatively quickly on the mountainside, normally in wet-wintery conditions¹¹⁸ and at high air velocities. Body heat is transferred more easily to water than it is in air, accidental immersion presenting a real hazard when activities take place in open seas, rivers, marinas or lakes, or enclosed caves.

Compared to adaptation to the heat, there is little physiological adaptation to the cold and so a behavioural approach towards limiting exposure to this environment becomes essential. Chronic exposure to cold air produces some adaptation¹¹⁹ but the emphasis on behavioural adjustment remains.

Altitude

Ambient pressure and the partial pressure of oxygen fall with altitude. The reduced supply of oxygen across the alveoli and the associated hypoxia do not become problematic until

the blood leaving the lungs is no longer sufficiently saturated. If this fall of saturation does take place, then the capability for physical activity becomes compromised. This impairment of activity, due to decreased maximal oxygen uptake, averages about 15% at 2200 m, although the blood of some individuals is not fully saturated at altitudes as low as 1500 m. Aerobic power declines progressively with increasing altitude, and so few sports events are held at altitude. This is illustrated by the ruling from the international governing body for association football (FIFA) that competitive matches cannot be held above an altitude of 2800 m without compromising the participants' health.

Altitude produces an increase in the depth and frequency of ventilation as well as tachycardia. The hyperventilation gives rise to a respiratory alkalosis, and this might give rise to bouts of dizziness. The kidneys excrete bicarbonate ions, and this adjustment corrects the alkalosis within a few days at moderate altitudes of 2000–3500 m. The kidneys also secrete the hormone erythropoietin, which promotes the release and maturation of red blood cells, this process taking 3–4 weeks. Travellers should have adequate iron stores in advance of the trip, as otherwise they will be unable to benefit from the increase in red blood cell production. A strategy that has enabled athletes to maintain the quality of training over this period entails sleeping at above 2500 m and conducting interval training 2–3 times weekly at about 1200–1500 m. This manipulation has become known as the "live high—train low" lifestyle.

As the altitude reached increases, acute mountain sickness may result and, higher still, an unacclimatised traveller risks pulmonary or cerebral oedema. The risk of these problems is more marked in those undertaking physical activity at altitude and in those who have some pre-existing respiratory or cardiovascular disorders. Travellers must be aware of the symptoms of these disorders, therefore, and be prepared to go back towards sea level, if necessary.

Alveolar oxygen tensions normally fall during sleep, but this drop is exacerbated at high altitude. Accordingly, sleep apnoea may be experienced. Hyperventilation, coupled with the dry ambient air causes dryness in the mouth, nose and throat, and general dehydration. Extra fluid intake is required to combat this, particularly as a diuresis is often present also. Glucose intake also should be increased to combat the greater utilization of glycogen as a fuel for activity under hypoxic conditions. Sports drinks can play a role in this respect.

Air pollution

The air in many of the world's large cities is regularly polluted. Pollution issues have arisen when such large metropolitan areas have hosted major sports events such as the Olympic Games. These cities have included Mexico, Los Angeles, Athens and Beijing as hosts of relatively recent Summer Olympics. Due to concerns about health-related consequences of pollution, it is now common practice to publish daily pollution values.

Pollutants can be classed as primary or secondary, depending on whether they change subsequent to emission. Sulphur dioxide, carbon monoxide, nitrogen oxides, benzene, lead and particulate matter such as dust and smoke are

primary pollutants. Particulates with a diameter of less than 10 microns (PM-10s) pose a pollution threat since they are small enough to penetrate to the alveoli. Secondary pollutants are generally formed by the action of ultraviolet radiation on primary pollutants, the major example of which is ozone.

The effects of air pollution on human performance have been reviewed by Florida-James et al.¹²⁰ They identified the major pollutants at Athens as nitrogen dioxide, ozone and PM-10s. Exposure to these pollutants causes a cough, chest pain, difficulty in breathing and headaches, the severity of the effects depending upon the amount of pollution and the duration of exposure. Effects of PM-10s are more marked in the elderly and in those with pre-existing lung diseases; healthy individuals are normally unaffected until the concentrations are high. Asthmatics are particularly vulnerable to adverse effects of pollution, and carrying their prescribed medications with them is of vital importance.

By counteracting the oxidative stress caused by ozone, antioxidant supplementation has been reported to reduce some of the effects of this pollutant¹²¹ but, otherwise, the only action that can be taken is to reduce exposure. Local authorities need to play an important role in this by reducing pollution due to vehicular traffic.

Concluding comments

It is clear that individuals must take environmental circumstance into account when planning a holiday or visit for training or competitive purpose. They must also be aware of the problems that might arise due to the daily vagaries of climate. The effects of different environmental stressors are likely to be interactive rather than additive, particularly with respect to inducing clinical symptoms that constitute a risk to health.

Conflict of interest

None declared.

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