ABSTRACT — Biological rhythms are an essential component of homeostasis: ‘everything is rhythmic unless proved otherwise’. Circadian (ca 24 h) rhythms are driven by an internal clock situated in the hypothalamus. Without time cues, they deviate from 24 h and assume a periodicity of, on average, 24.3 h. Periodicity is inherited, and progress has recently been made in identifying ‘clock’ genes. Circadian rhythms are synchronised to the 24-h day mostly by light-dark cycles and social time cues. Suitably timed bright light and the pineal hormone melatonin will change the timing of circadian rhythms and can be used to treat biological rhythm disorders, whether occupational or pathological. Rhythm disorder is usually manifested as sleep problems, but some major pathology (eg cardiovascular disease) is associated with frequent rhythm disruption as found in shift workers. Menstrual cycle variations are clearly of importance, and even human seasonality must be taken into consideration. Many drugs show rhythmic variations in pharmacokinetics and pharmacodynamics. Exploitation of this phenomenon, together with underlying target tissue sensitivity, is underway.

In early medical texts doctors clearly recognised the importance of biological rhythms. The remarkable daily and seasonal prevalence of certain illnesses and/or exacerbation of symptoms were carefully described. Today, we know that certain diseases are a direct result of abnormal function of the internal biological clock and/or the perception of factors that regulate it. We also know that therapeutic intervention can sometimes be more or less successful depending on, for example, the time of day of medication. The numerically and economically most important aspects of biological rhythm problems probably concern the 25% of the population of any developed country who work night shifts, and the related phenomenon of jet lag. In keeping with the trends of modern medicine, ‘clock’ genes have been identified in mammals, and molecular dissection of mechanisms proceeds apace. This review considers these areas, and aims to extract sufficient practical clinical information to permit readers to judge the actual and potential usefulness of a ‘rhythmic’ approach.

Ubiquitous rhythms

Biological rhythms of various periodicity occur in all eukaryotic organisms and are an essential component of homeostasis. They display frequencies varying from fractions of a second (eg firing of neurons) to years (eg population variations). By far the most information is available concerning daily rhythms. Rhythms with a periodicity of less than a day are known as ultradian (eg pulse rate, pulsatile secretion of hormones) and of more than a day as infradian (eg menstrual cycle). Rhythms corresponding to major periodicities in the external environment (daily, annual) are the most prominent.

Rhythmicity is important to health in a variety of ways. Sleep-wake is the most obvious of the daily behavioural rhythms, with its accompanying increase in the ‘darkness’ hormone melatonin, prolactin and growth hormone, and drop in core body temperature. The plasma levels of many hormones vary with sleep stages. Mood varies during the day, usually being at its lowest in the early morning. Alertness rises during the course of the day. The ability to perform various tasks has a daily variation, with a minimum during the night coincident with the nadir of core temperature and the maximum of melatonin and perceived fatigue. The early morning rise in blood pressure and the stress hormone cortisol, and the reduction of urine volume at night are yet other examples. Although all these are well known, it is perhaps less appreciated that pancreatic and metabolic functions also vary during the 24 hours. Glucose tolerance decreases during the day and there is evidence for insulin ‘resistance’ during the night. There are pronounced rhythms in gastric emptying and in at least some gastrointestinal (GI) hormones (not all have been studied from this point of view). The immune system shows striking daily and seasonal variations. Most neurotransmitters and their metabolites show diurnal changes. At the cellular level, there are variations in cell proliferation, DNA synthesis and enzymes concerned with metabolism. The pharmacokinetics and pharmacodynamics of many drugs show changes, in some cases huge, in the course of the 24-h cycle. Eighty per cent of asthma attacks occur at night, and deaths from cardiovascular disease are more likely to occur in the morning, to cite but two examples of rhythmicity in disease.

Humans also show seasonal rhythms, although rigorous demonstration of such rhythms is often lacking. Apart from variations in the incidence of viral infections, probably the best known example is the so-called seasonal affective disorder (SAD) or winter depression. Suicides, however, peak in the spring, with a secondary peak in autumn – interestingly, a similar pattern to that of the conception rate in Europe. Seasonality is apparent in the detection of some cancers and, indeed, in general mortality. It would not be unreasonable to state that everything is rhythmic unless proved otherwise.

Only some of the above cited daily rhythms have been shown to be truly endogenous — that is, generated within the body and controlled by a master rhythm generator referred to as the biological clock. It is in the area of clock function that most progress has been made in recent years and to which most of this review is addressed.
The importance of internal rhythms in clinical medicine lies in two areas:

1. Where the internal clock is, for various reasons, at odds with the environment and with social and professional requirements. In this case, strategies for adjusting the clock can be envisaged.

2. Where treatment, and to some extent diagnosis, depend on time of day (and possibly on time of menstrual cycle and time of year). Time of day effects can be harnessed to improve outcomes. Most recent information concerns clock-shifting techniques.

In order to understand and apply strategies for shifting the clock, some basic rhythm theory is required.

The biological clock

Rhythms may be externally imposed, internally generated or, more frequently, determined by a combination of these two factors. Internally generated daily rhythms are known as circadian (approximately a 24-h period, from the Latin ‘about a day’). Circadian rhythms programme the daily sequence of metabolic and behavioural changes, and may also serve as reference points for annual changes.

A rhythm displaying its endogenous period in the absence of time cues is said to be ‘free-running’ and is desynchronised from environmental periodicity. Endogenous rhythms are driven by a pacemaker (oscillator, biological clock). The manifested endogenous period depends on species, individuals, conditions and previous history, and is an inheritable characteristic. Most is known about ‘clock’ genes in fruit-flies and fungi, but a gene (Clock) that controls periodicity has also been identified in mice. This locus was mapped to chromosome 5, a region syntenic to chromosome 4 in humans. Although Clock-controlled events are specific to the biology of the species in question, in general it is thought that common cellular mechanisms are conserved, and that insights gained from work on unicellular organisms will provide the basis for understanding the cellular mechanisms of human clocks. At the molecular level, there is substantial evidence that the basic circadian oscillator is a feedback loop. Expression of putative Clock genes is high when levels of their products are low. Build-up of gene products in the cytoplasm, followed by entry into the nucleus, inhibits transcription. In the absence of transcription, levels of mRNA and product decline, allowing transcription to restart about 24 h later in the case of a circadian Clock gene (Fig 1). Evidence for rhythmic gene expression and inhibition of expression by product has been established experimentally for the per (fruit-flies) and frq (Neurospora crassa) clock genes. Moreover, in the case of frq, light pulses reset the expressed rhythm by inducing frq expression and overriding negative feedback regulation by gene products. The cellular and molecular mechanisms of biological clocks have recently been extensively reviewed.

The major biological clock in mammals is situated within the suprachiasmatic nucleus of the hypothalamus (in some birds and lower vertebrates the pineal gland is the principal rhythm generator). Removal of this area leads to loss of virtually all circadian rhythms. The environmental factors that entrain or synchronise a rhythm to a given periodicity are referred to as zeitgebers (time-givers or time cues) (Fig 2). Humans show free-running circadian rhythms that are usually longer than 24 h (on average, 24.3 h).

The most important time cue that affects synchronisation to the environment is the light-dark cycle. Social cues, regularly timed meals and knowledge of clock time also play a role. If the endogenous period of a circadian rhythm is greater than 24 h, synchronisation requires a phase advance of the clock each day by this amount; if less than 24 h, the clock must be delayed each day.

Fig 1. Cellular mechanisms of clock function derived from studies in Neurospora. The basis of the Clock is a feedback oscillator whereby Clock gene expression is inhibited by Clock gene products. The oscillator keeps time with a steady period length and is independent of changes in temperature and the metabolic environment. In the case of frq, there is evidence that the FRQ protein downregulates frq mRNA and transcriptionally regulates the rhythmic activation of Clock controlled genes (adapted from further reading 19).
Problems associated with occupational circadian rhythm disturbances

Sleep and performance

The most obvious manifestation of disturbed circadian rhythms is disturbed sleep. Sleep is of greater duration and better quality when it occurs during the falling phase of the core temperature (endogenous) rhythm and the rising phase of melatonin production. Core temperature and melatonin shift slowly in response to changing time cues. Shift workers, even those doing permanent night shift work, rarely adapt their clock to be in tune with their behaviour, so that night shift workers are attempting to sleep as their core body temperature rises in the morning and to work at the nadir of their performance and the peak of their fatigue rhythms (Fig 3). The degree of shift in night shift workers may depend on their exposure to early morning natural bright light (acting counter to the direction of adaptation), with greater exposure associated with less adaptive shift of hormonal markers. Several major accidents (Chernobyl, Three Mile Island, Exxon Valdez) have been attributed to problems of night shift work, and there is a generally higher incidence of accidents on the night shift.

After flying over eight time zones westwards, say from the UK to Los Angeles, it is a common experience to wake exceptionally early (say, at 2 am) and be unable to sleep thereafter. During the following days, waking occurs progressively later until it coincides with local time. Performance suffers similarly to that of shift workers. Going eastward, it is the long latency to sleep and oversleep/tiredness in the morning that cause problems. Not all subjects experience these effects to the same degree for reasons that are presently unknown.

Gastrointestinal problems

The second most common complaint is GI disturbances: indigestion, heartburn, irritable bowel syndrome and defaecation at odd times. In shift workers, this might to some extent be ascribed to diet, but recent evidence suggests that unadapted endogenous rhythms are of major importance.

Major disease

It is difficult properly to evaluate the mortality rates in comparable populations of shift and non-shift workers, in long- and short-haul pilots, and in frequent fliers and non-fliers. Intolerant subjects deselect themselves. It was shown many years ago that frequent time-zone shifting led to early death – but this was in fruit-flies. However, shift workers have a higher than normal incidence of cardiovascular disease and also show evidence of lipid intolerance and greater prevalence of non-insulin-dependent diabetes. Against this is the fact that long-haul pilots...
apparently live longer than the general population, although their high standard of living and careful frequent medical evaluation make this observation of little significance to the population in general.

Abnormal function of the endogenous clock

Circadian related sleep disorder

A number of circadian related sleep disorders have been documented and officially coded in the International Classification of Sleep Disorders. They include:

- delayed sleep phase syndrome, where subjects are unable to sleep before 2-3 am and have difficulty awakening before late morning;
- sleep onset insomnia, with normal awakening time;
- advanced sleep phase syndrome, where subjects fall asleep very early and wake long before dawn;
- early morning awakening with normal sleep onset – this and the previous disorder are found frequently in the elderly;
- non-24-hour sleep-wake syndrome, often found in blind subjects and rarely in sighted people;
- gross arrhythmicity of the sleep-wake cycle, which is very rare and generally due either to a lesion in the clock itself (eg a tumour in the area of the suprachiasmatic nucleus of the hypothalamus) or to disturbed sleep regulation such as fatal familial insomnia.

Narcolepsy, however, does not appear to be related to a clock disturbance. Sleep duration disorder includes the hypersonnia of SAD, but is not conclusively linked to disturbed clock function.

Blindness

According to a recent epidemiological study, 58% of registered blind subjects in the UK appear to suffer from sleep disorder, as assessed by the Pittsburgh Sleep Quality Index, with greater prevalence in individuals who have no conscious light perception. These disturbances vary from delayed sleep phase syndrome to irregular phase position, to some with free-running circadian rhythms in a normal environment. The last is usually, but not invariably, associated with complete lack of light perception, and specifically ‘hypothalamic’ light perception. In most subjects, poor sleep corresponds to the anti-phase of the endogenous melatonin rhythm. The situation is thus analogous to jet lag and shift work whereby subjects intermittently have to sleep at an inappropriate circadian phase.

Psychiatric disorder

Many features of affective disorder are linked to biological rhythmicity. Diurnal variation in symptom severity (worse in the morning) is a characteristic feature of depression. Depression and manic depressive disorder are recurrent phenomena, in approximately 15% of cases recurring on a seasonal basis. Rapid cycling from mania to depression and vice versa has frequently been reported. Depression is often associated with changed patterns of sleep, appetite and weight: in ‘endogenous’ depression patients sleep and

Fig 3: Two major circadian rhythms, core temperature (°C, measured in a ‘constant routine’) and melatonin (pg/ml) are closely inversely related. The night-time rise in melatonin may be responsible for part of the temperature decline. The peak time for fatigue and accidents in night shift work corresponds to peak melatonin and the nadir in core temperature. Both rhythms shift slowly in response to abrupt changes in time cues such as in shift work.
eat less, whereas in atypical depression (eg SAD) they sleep and eat more. Seasonal forms of the illness can be triggered by environmental changes, especially light intensity and duration. Sleep changes with depression and mania may be both causally and consequentially related to the disease process. However, in spite of all these suggestive observations, there is no good evidence for a basic malfunction in the biological clock in psychiatric disorder.

**Old age**

A decline in circadian function is evident in many studies of the elderly. A marked lowering in the amplitude of the melatonin rhythm and that of a number of other variables has frequently been reported, together with an earlier timing of some rhythms, especially sleep. Sleep may also become fragmented at night, with increasing daytime naps. Although this may relate to declining function of the clock, a more general explanation relates to perception of the time cues that maintain integrity and synchronisation of rhythms. The amount of light reaching the retina decreases as ageing lenses become discoloured. Decreasing physical activity, more time spent indoors, possibly irregular meals and reduced social contact, would all conspire to loosen synchronisation within the body and with the environment.

**Strategies for treating disturbed clock function**

**Light and melatonin**

Provided that the internal rhythm generating system is intact, various methods can be employed to shift and resynchronise body rhythms. Bright light is the strongest time cue available. The importance of light to human physiology has only recently been appreciated with the demonstration (in 1980) that light of over 2,000 lux was required to suppress melatonin (the darkness hormone) secretion at night. Domestic intensity light is around 300-500 lux, and natural full sunlight can reach 100,000 lux. Subsequent experiments have confirmed the immense importance of light to human physiology; most particularly, that bright light of suitable intensity, timing and duration will both advance and delay the circadian clock in humans. This phenomenon is usually expressed as a phase response curve. A light pulse (3-5 h, 2,000-10,000 lux) given during the period before the minimum of core temperature will delay the clock; given during the period after core temperature minimum it will advance the clock. In simpler terms, this means that bright light during the late evening will delay, and in the early morning advance, the clock in a subject who is normally synchronised to the 24-h day. The pineal hormone melatonin is the complementary internal time cue. It signals the length of the night in animals, and this information is used to time both daily and seasonal rhythms. In humans, it will shift rhythms. The phase response curve to melatonin is opposite to that of light: melatonin in the early evening will advance, and in the early morning delay, circadian rhythms. Both light and melatonin have acute effects on physiology:

- bright light at night increases core body temperature and alertness
- melatonin during the day decreases core temperature and alertness and can induce transient sleep, depending on dose.

These acute effects and cumulative phase shifts can be employed in adapting to phase shifts. It is likely that in a normal environment light and melatonin act in concert to maintain circadian synchrony. It also appears that exercise, social cues, set meal times and knowledge of clock time can sometimes be effective time cues in the absence of any light perception.

**Drug therapy**

In addition to these naturalistic treatments, a number of drugs will modify the circadian system; for example, lithium and the monoamine oxidase inhibitor clorgyline lengthen the period of free running rhythms, desipramine and moclobemide shorten it. Vitamin B₁₂, which has the ability to synchronise rhythms in some subjects, may work through sensitisation to light.

**Successful therapy**

Chronobiology is in its infancy, and the number of reported therapeutic interventions small, but some estimate of current success and future potential can be given. There is only a limited amount of information concerning light and melatonin as interventions. It is evident that light and/or melatonin must be timed to advance or delay the circadian system, as appropriate. For jet lag this will depend on direction of travel and number of time zones crossed, and for shift workers on the type of shift schedule. In order to time treatment correctly, it is essential to know the circadian status of the subject. In normal subjects synchronised to the environment, this can to some extent be judged by habitual sleep times, but it is not so simple to judge for frequent long-haul fliers who are constantly shifting time zones. Ideally, a robust, rapid, non-invasive method of assessing, for example, melatonin or core temperature phase position (the best rhythm markers) would be ideal but does not yet exist.

**Shift work**

Bright light and its avoidance may be useful in helping workers adjust to shift work schedules by facilitating phase shifts of circadian rhythms, although little work has been conducted in real-life shift work settings. A few laboratory simulation and field studies have measured circadian phase after bright light (2,000-12,000 lux) or dim light.
during the night shift combined with imposed darkness during sleep time. The general finding has been that circadian rhythms shifted about 1 h/day in the dim light conditions, and as much as 2–4 h/day in the bright light conditions. Sleep problems abated and performance improved as body temperature minimum shifted to align with sleep time. Recent evidence suggests that GI function can also be improved by phase-shifting strategies.

Studies to examine the use of bright light for real shift (as opposed to simulated shifts in the laboratory) workers have been conducted at the National Aeronautics and Space Administration (NASA) and in Antarctica. NASA has employed timed exposure to bright light to help both space shuttle astronauts and ground crew to adjust to night shifts, and the bright light phase-shifting procedure has become a permanent part of the shuttle programme. However, the desired results have not been obtained in all studies, and puzzling results have been obtained in some. Much basic research is still needed, particularly to define the precise amount and timing of light needed to help adaptation.

There is little published work on the use of melatonin in real shift work. Any effects on work-related performance need careful evaluation. It is not always desirable, for example in rapidly rotating shifts, to adapt the circadian system since sleep and activity on rest days will be compromised. In these circumstances, the acute effects of melatonin may be useful rather than its phase-shifting ability. Two reports describe improved sleep and some adaptation of circadian rhythms in field studies.

Jet lag

Scheduled exposure to bright light can, in principle, alleviate the symptoms of jet lag by accelerating circadian re-entrainment to new time zones. Only a small number of field studies, all preliminary, has been conducted to examine the efficacy of bright light treatment. Thus far, they have yielded encouraging results, but their applicability to the population at large remains uncertain due to limited sample sizes.

For aircrew scheduled to return to home base after brief layovers, staying on home time may be preferable to trying to adjust to local time, thus eliminating the need for re-adjustment after the return flight. In such cases, bright light treatment may be used to maintain entrainment to home time rather than to accelerate re-entrainment to new local times.

Administration of melatonin, timed pre-shift to initiate a phase advance and post-shift to reinforce this, has been used successfully in comparison to placebo to adapt to simulated nine-hour advance shifts of the light-dark cycle. Improved alertness, performance and sleep parameters, and faster adaptation of some other rhythms have been found, together with some inconsistent effects on sleep. Melatonin could also counter some inappropriate bright light exposure. The latter observation suggests that melatonin will be useful in field conditions, even when night shift workers are exposed to bright light on their way home in the morning.

Thus far, melatonin has been used successfully to alleviate perceived jet lag (primarily sleep disturbance) in at least five placebo-controlled field studies. Most studies have used pre-flight administration in the evening to initiate a phase advance eastward, with post-flight administration at bedtime to reinforce the advance. Westward pre-flight administration in the early morning to initiate a delay can be a nuisance for subjects who feel sleepy after melatonin, and administration only post-flight has been successful. One study in aircrew reported problems with pre-flight (3 days) melatonin administration but improvement with only post-flight treatment. Long-haul aircrew are constantly undergoing phase shifts of local time cues and, as the timing of melatonin is fairly critical, it is not unlikely that subjects received the pre-flight treatment at an inappropriate circadian phase.

The last analysis of current field studies (Arendt et al; unpublished data) on the alleviation of self-rated jet lag by melatonin included 474 subjects taking melatonin (5 mg in a lactose-gelatine capsule) and 112 taking placebo (Fig 4). Overall, there was a 50% reduction of self-rated jet lag. Side effects reported more than once are listed in Table 1. If it were possible to time treatment more precisely according to individual circadian phase in field conditions, it is possible that even better results would be obtained.

Sleep problems in blindness, old age and other conditions

Only a small number of subjects has been studied, but so far most blind subjects with sleep problems derive some benefit from timed melatonin treatment. The major effect is a stabilisation of sleep onset. A group of children with multiple disabilities, mostly visual defects, behavioural and sleep problems, were successfully treated with melatonin. The reported benefit derived in these studies was truly impressive.

Both early morning bright light exposure and evening melatonin treatment have been successfully employed to advance sleep time in delayed sleep phase syndrome. Maintenance of the effect is not simple as these subjects are 'night owls' and their habits require radical revision. Only single case reports exist of evening bright light for advanced sleep phase syndrome in young adults.

Although studies are limited, results strongly suggest that evening bright light exposure is beneficial in alleviating sleep maintenance insomnia in healthy elderly subjects. Less consistent, but generally positive, findings have been reported also with regard to bright light treatment of sleep and behavioural disturbances in demented patients. No study has yet examined the long-term benefits of bright light treatment for age-related insomnia. This is a critical area of investigation, since sleep disturbance in older populations is usually a chronic disorder.

Improved sleep in the elderly taking low-dose melatonin
The tonin has likely pharmacological cues circadian with Bright evident melatonin normalises sleepiness. Side effects may include headache, light-headedness, 'fuzziness/giddiness', and 0.6% hypercortisolaemia, 0.8% glucose intolerance, and 0.9% blood pressure changes.

Receptors and analogues

The melatonin receptor has been cloned. It is present within the central biological clock in humans and most other species (other sites include other brain areas, the pituitary stalk and the femoral artery). This has stimulated considerable interest among pharmaceutical companies. A number of agonists and antagonists (chemical light) are under development, and the next few years should see some interesting new applications and even licensed products on the market.

Chronopharmacology, diagnosis and surgical intervention

Problems that can be traced back to the generation (suprachiasmatic nucleus) and synchronisation (time cues) of rhythms must be distinguished from those for which there is yet no evidence of internal clock problems, such as variation in drug pharmacokinetics and pharmacodynamics (discussed in the following section).

Internal circadian time and clock time are not the same. This is evident when considering a free-running blind person whose maximum sleep propensity has moved to the middle of the day rather than the middle of the night. Physicians generally treat patients either without regard to time of day or at a specific time of day. Thus, even normally phased individuals may receive treatment at slightly different circadian times, and patients with clock problems may receive treatment at completely inappropriate circadian times. Similarly, when diagnosing, for example, hypercortisolism, glucose intolerance or high blood pressure, circadian time is of importance in the result obtained. In general, this means that patients who
work night shifts or who have recently crossed a large number of time zones may give anomalous results.

**Pharmacokinetics and pharmacodynamics**

The handling of drugs is subject to a multitude of rhythmic variations in absorption, distribution, metabolism and elimination that ultimately determine plasma and target tissue concentrations. Tissue sensitivity to drug action likewise depends on numerous rhythmic factors, of which rhythmic variations in DNA synthesis and cell division are probably the most important. Circadian variation in drug metabolism and tissue sensitivity to drugs predictably modulate toxicity and effectiveness. Evidence is accumulating that therapy can be improved and toxicity reduced by administering drugs at carefully selected times of day.

**Cancer**

Much research, especially in the USA, has concentrated on cancer chemotherapy where destruction of malignant cells often depends on the use of highly toxic interventions. Most cancer drugs damage more severely actively reproducing cells than those that are not dividing. Regular circadian rhythms in bone marrow and GI tract cell division may partly explain the time-of-day dependent toxicity of cell cycle active anticancer drugs. Each cancer investigated to date requires a specific strategy. If tumour cells are most susceptible to destruction at a time when host cells are resistant, the approach is obvious. If tumour cells have no or weak daily variation in susceptibility, treatment should be timed at the minimum of host toxicity. A long-term study of carefully timed doxorubicin/cisplatin treatment of ovarian cancer according to the above principles has shown that five-year survival was greatly improved by morning doxorubicin and cisplatin 12 h later (44% survival) compared to morning cisplatin and evening doxorubicin (11% survival) (Fig 5). Most of the data have been summarised in a recent review which gives recommendations. Newer results with growth factors (granulocyte-macrophage colony stimulating factor and erythropoietin) demonstrate that optimal circadian timing leads to 1-1½ orders of magnitude improvement in their therapeutic efficiency.

**Asthma, peptic ulcer and hypertension**

**Asthma.** Theophylline was one of the first drugs for which daily pharmacokinetic variations were reported. By international consensus, it needs to be administered in higher doses during the evening to overcome symptoms of nocturnal asthma. Sustained-release preparations are available for evening use. Similar considerations apply to β2-agonists.

**Peptic ulcer.** For the treatment of peptic ulcer disease, it is unanimously recommended that H2-blockers should be taken once a day in the evening to overcome night-time gastric hyperacidity.

**Hypertension.** In both normotension and primary hypertension there is a nightly drop in blood pressure. In forms of secondary hypertension found in renal disease, hyperthyroidism, pregnancy or Cushing’s disease, the blood pressure rhythm may be abolished or reversed, with high values at night. There is some evidence that once-daily dosing with beta-blockers and calcium channel-blockers is more effective during the day than at night. The German Medical Association has recently recommended that antihypertensive drugs for primary hypertension should be given in the early morning, whereas for secondary hypertension a second evening dose may be required.

**Infradian and ultradian rhythms**

In addition to these essentially circadian approaches, there is a substantial literature concerning the importance of infradian (menstrual) and ultradian (pulsatile-episodic) rhythms in diagnosis and therapy. For example, for induction of ovulation in some types of infertility, administration of luteinising hormone-releasing hormone should be pulsatile (ie mimic the natural production during the menstrual cycle). Insulin has a high-frequency pattern of release associated with an inverse pattern of blood glucose underlying its response to nutrients. It has been suggested that if it were possible to deliver insulin in this way, diabetic end-organ disease might be diminished. Many other hormones have pulsatile release, and this approach merits attention.

A great deal of publicity was attached to reports that the timing of breast cancer resection within the menstrual cycle influences the outcome, with a better prognosis if
surgery takes place during the luteal phase of the cycle. Whilst there are almost as many (retrospective) reports that timing does not affect outcome, an interesting recent observation suggests that tumour epidermal growth factor levels are higher during the follicular phase of the cycle. This may provide a rationale for further work.

Conclusions

Although the results of many years of research involving both animals and humans demonstrate unequivocally that timed exposure to bright light or melatonin is an effective means of manipulating the circadian timing system, it appears that many more years will be needed to develop effective, reliable and practical treatment strategies.

The observations reported here represent the tip of an iceberg. The time dimension has barely become respectable in clinical medicine, even though it is an essential component of homoeostatic mechanisms. It is obvious from the brief section on chronopharmacology that drug development should take time into account. At present, the vast majority of drug development studies use the nocturnal rat – moreover, with acute administration during the daytime (i.e. the rat's night). How much time, effort and money have been wasted in this way we shall probably never know. It is almost unbelievable that drugs should be first tested in the middle of the (rat's) night when they are (mostly) destined to be used in the human day.

Further reading

1 Arendt J. Melatonin and the mammalian pineal gland. London: Chapman Hall, 1994.
2 Arendt J. Melatonin: claims made in the popular media are mostly nonsense. Br Med J 1996;312:1996-7.
3 Aschoff J, Daam S, Gross G (eds). Vertebrate circadian systems. Berlin: Springer-Verlag, 1982.
4 Belanger P. Chronopharmacology in drug research and therapy. Adv Drug Res 1993;24:1-80.
5 Cassone V. Effects of melatonin on vertebrate circadian systems. TINS 1990;13:457-63.
6 Crosthwaite SK, Loros JJ, Dunlap J. Light-induced resetting of a circadian clock is mediated by a rapid increase in frequency transcript. Cell 1995;81:1003-12.
7 Hastings M. Resetting the circadian cycle. Nature 1995;376:296-7.
8 Wehr TA, Wirz-Justice A, Arendt J, Campbell S, et al. Clocks and human biology. In: Dunlap JC and Loros JJ (eds). The circadian biological clock (in press).
9 Klein DC, Moore RY, Reppert SM (eds). Suprachiasmatic nucleus, the mind's clock. New York: Oxford University Press, 1991.
10 Knutsson A. Shift work and coronary heart disease. Scand J Med Soc 1989;44(Suppl):1-36.
11 Chronobiology. In: Kryger MH, Roth T, Dement WC (eds). Principles and practice of sleep medicine. Philadelphia: WB Saunders Co, 1995:277-330.
12 Disorders of chronobiology. In: Kryger MH, Roth T, Dement WC (eds). Principles and practice of sleep medicine. Philadelphia: WB Saunders Co, 1995:463-85.
13 Terman M. Light treatment. In: Kryger MH, Roth T, Dement WC (eds). Principles and practice of sleep medicine. Philadelphia: WB Saunders Co, 1995:1012-29.
14 Levi F, Reinberg A, Canon C. Clinical immunology and allergy. In: Arendt J, Minors DSM, Waterhouse JM (eds). Biological rhythms in clinical practice. London: Wright, 1989:99-135.
15 Oliver DJ, Ingram DM. Timing of surgery during the menstrual cycle for breast cancer: possible role of growth factors. Eur J Cancer 1995;31A:325-8.
16 Rosa RR, Bonnet MH, Bootzin RR, Eastman CI, et al. Intervention factors for promoting adjustment to nightwork and shiftwork. Occup Med: State of the Art Rev 1990;5:391-415.
17 Touitou Y, Haus E (eds). Biological rhythms in clinical and laboratory medicine. Berlin: Springer Verlag, 1992.
18 Wehr TA, Rosenthal NE. Seasonality and affective illness. Am J Psychiatry 1989;146:829-39.
19 Loros J. The molecular basis of the Neurospora clock. Sem Neurosci 1995;7:3-13.
20 Arendt J, Deacon S, English J, Hampton S, Morgan L. Melatonin and adjustment to phase shift. J Sleep Res 1995;4(Suppl 2):74-9.
21 Hrushesky WJM. Circadian timing of cancer chemotherapy. Science 1985;228:79-5.

Address for correspondence: Josephine Arendt, Professor of Endocrinology, School of Biological Sciences, University of Surrey, Guildford, Surrey GU2 5XH.