In the general-practice setting cognitive therapy was claimed to be superior to drug treatment. This is certainly a provocative conclusion, but it is based on rather scanty data. Only seven patients received drug treatment only from their family doctor, and in this group the improvement in symptoms reported was curiously low. The mean percentage change score for the Beck Depression Inventory in the general-practice setting was 84% for patients who had had cognitive therapy, but only 14% for those who had had drugs. Previous research in general-practice settings cannot be compared directly since it has not used percentage change scores, but about two-thirds of psychiatric illnesses seen by general practitioners can be expected to have remitted at six months[7] or 12 months[8] when treated by methods that do not include cognitive therapy.

In an ideal study all patients would receive both a psychological treatment and a tablet (active drug or placebo), a simple 2×2 factorial design being used; and the assessors would be blind to which treatment the patient was getting. Cognitive therapy could be compared with one of the alternative psychological treatments for depression, such as Weissman's Interpersonal Psychotherapy.[9] Such a study would enable firm conclusions to be drawn concerning the value of those therapeutic procedures that are specific to cognitive therapy.

Despite the potential importance of cognitive therapy, probably most depressed patients will continue to be offered drugs. Prescribing a drug takes very little professional time and is much easier than cognitive therapy. Depression is a common condition, and cognitive therapists are scarce. General practitioners and physicians are unlikely to wish to learn such specific techniques unless they have a particular interest in psychotherapy, so even if the technique becomes established they will presumably wish to refer patients to colleagues who have undergone special training. If the present promising results with cognitive therapy are confirmed they will have implications for a wide range of training schemes, and will once more direct our attention to psychological treatments for psychological disorders.

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Regular Review

Physiological changes underlying jet lag

JOSEPHINE ARENDT, VINCENT MARKS

Each year millions of travellers experience a temporary loss of sleep, discomfort, and reduced efficiency after rapid travel across several time zones—the experience commonly known as "jet lag." In no way is jet lag associated with serious illness in normal people, but after transmeridional flight major body functions such as sleepiness, hunger, and defecation may intrude at inappropriate times for variable periods. Disturbances of biological rhythms are generally accepted as largely responsible for the observed effects. Since, however, deprivation of sleep is a major complaint among jet-lagged travellers loss of sleep by itself may be a factor in impaired performance.

Biological rhythms are not to be confused with the discredited so-called biorhythms of a 23-day physical cycle, a 28-day emotional cycle, and a 33-day intellectual cycle,[1] which have given rise to calculators to pinpoint propitious or unpropitious days according to the individual's date of birth. The existence of biological rhythms is verifiable by experiments and they are found in all species from unicellular organisms to man, and with frequencies varying from fractions of a second (for example, the firing of nerve fibres) to years (for example, variations in population). Major biological rhythms coincide with geophysical events in the environment: the daily light-dark cycle, the lunar and tidal cycles, and the seasonal cycle. Many rhythms have been shown to continue even in the absence of environmental cues or "zeitgebers" (time givers), but with periods slightly different from the environmental period—hence the term circadian (*circa*, about; *dies*, a day) for daily rhythms which continue, or free run, in isolation. In view of this endogenous nature of many rhythms, organisms are thought to have developed an internal model of external time, usually referred to colloquially as the biological clock.

The major daily cycles in man (that is, those relating to rest-activity (sleep-wake), temperature, rapid eye movement sleep, excretion of electrolytes, and production of cortisol) have been

studied intensively to determine whether they show endogenous rhythmicity in the absence of periodic input from the environment. Studies in specially constructed isolation bunkers, notably by research groups led by the late Professor John Mills (Manchester University, Department of Physiology) and Professor Jürgen Aschoff and Rütger Wever (Max-Planck Institut für Verhaltensphysiologie, Erling-Andechs, West Germany) show that in most persons cortisol production, temperature, and the sleep-wake cycle are among those that continue to oscillate, but with a lengthened period of about 25 hours.[2-4] In some individuals, however, the sleep-wake cycle may assume a much longer period (for example, 33-50 hours) though the temperature rhythm remains around 25 hours.[5,6] Such individuals are said to be "internally desynchronised." The simultaneous presence of two different periods in major rhythmic functions has been taken as evidence that at least two major oscillators control body rhythms and that they are normally coupled together, possibly through a master biological clock itself entrained by environmental cues. In rats all the biological rhythms so far studied can be eliminated by destroying the suprachiasmatic nuclei of the hypothalamus,[7] which is the most likely candidate for the site of the hypothetical master biological clock in mammals.

In normal conditions many external cues can provide signals or zeitgebers for the entrainment of rhythmic function. The light-dark cycle, temperature variations, social cues, and, in man, knowledge of clock-time are of particular importance. The range of frequency to which, for example, a 24-hour rhythm can be rapidly entrained is, however, limited, and it is this fact that leads to the rhythmic disturbances found in travellers across time zones. A five to six hour time difference encountered on crossing the Atlantic, for example, is beyond the normal range of entrainment; the endogenous circadian system is forcibly desynchronised and the various components require different lengths of time (from days to weeks) to become re-entrained to local time.[8]

The time taken for adjustment of rhythms after westward flight is known to be somewhat less (some authors quote 50% less) than that after eastward flight. This directional asymmetry is commonly explained by the fact that the endogenous circadian system naturally adopts a longer day (about 25 h) in isolation and hence would tend naturally more rapidly to accommodate the longer day (phase delay) required by westward flight. Some confusion exists on this point, however, as during simulated time zone shifts a more rapid eastward adjustment has sometimes been seen.[5] Wever[5] has suggested several reasons for these discrepant observations, including the deprivation of sleep and emotional stress that may occur with real, but not with simulated, flight, and the use of different time-bases for reporting the experimental data.

The known potential for the sleep-wake cycle to be dissociated from the approximately 25-hour endogenous circadian period may explain how the sleep-wake cycle rapidly adjusts to local time zone shifts and indeed is frequently helped to do so by the use of hypnotics. Other rhythms, however, such as temperature and cortisol, lag by a variable number of days, and until the whole system is restabilised the individual is effectively in a state of desynchronisation. How important this desynchronisation is for wellbeing is a matter for debate.

Manic-depression and unipolar depression are both accompanied by disturbance of rhythmic function.[9] The temperature/rapid eye movement/cortisol cycles (which are closely coupled with each other) and the sleep-wake cycle appear to be synchronised in an abnormal phase-relation in these disorders, similar to that found shortly after east-west flight. Whether this abnormality plays any part in their causation is still controversial. A recent report by Wehr and his co-workers reinforces the idea that the phase-relation of the rhythms is important: in one depressive patient they found that phase-shifting the sleep-wake cycle alone could induce temporary remission.[10]

Aircrew do not show any specific sickness trends, however, and shift workers (who work in an analogous way) do not have a higher mortality than the general population.[3] Both groups are highly selected, and those individuals capable of adapting to shifting flight or work schedules may be particularly robust in their bodily rhythm characteristics. Reports of menstrual disturbances in air hostesses are contradicted by others showing a stabilisation in the course of long-term exposure to time-zone shifts.[11]

Clearly, when hormone secretions are inappropriate to the time of day these may have profound, if temporary, physiological consequences. One understudied example of this is the considerable variation in the plasma insulin and blood glucose response to a meal eaten at different times of the day and the problems this may give rise to in the diagnosis of diabetes.[12] Another matter for concern is the effect of drugs. Both their pharmacodynamic effects and pharmacokinetics may vary dramatically according to the time of administration. This much neglected aspect of pharmacology could have serious implications in the treatment of time-zone travellers.[13-15]

Published material on biological rhythms in man has been expanded recently by a monumental study by Désir *et al*[16,17] of the hormonal changes underlying jet lag after a real-flight time-zone shift of seven hours, first westwards and then eastwards 30 days later, in the same group of five normal, healthy volunteers. Blood was sampled at 15-minute intervals for 25 hours on several days before and after each flight. In addition to the usual measurement of pituitary-adrenal cyclicity, the study included the changes in the rhythmic production of the pineal hormone, melatonin. Pineal melatonin production is of particular interest as a rhythm marker in circadian rhythm studies, as it is linked in the rat,[18] and probably also in man, by neural pathways to the suprachiasmatic nucleus. It is entrained by the light-dark cycle, being suppressed by light and stimulated by dark, though in man it is refractory to acute suppression by normal intensity (as opposed to very bright) artificial illumination in healthy individuals.[19,20] The rhythmicity of secretion of melatonin is also remarkably resistant to minor stresses, metabolic variations, and other manipulations of its rhythmic production.

In the study by Désir and colleagues[16,17] some aspects of ACTH-cortisol secretion took up to three weeks to adapt to local time westwards but only 11 days eastwards. In contrast, and in line with most previous findings, there was greater subjective discomfort, perturbation of sleep (after longer sleep deprivation), and disruption of the secretory rhythm of melatonin after the eastward flight. While the pattern of sleep disruption was highly correlated with psychological stress, assessed by ratings of anxiety and depression, there was no correlation between subjective discomfort and ACTH-cortisol periodicity. Indeed, normal sleep and low rating of anxiety and depression were observed with complete desynchronisation of the ACTH-cortisol rhythm. Overall this study serves to underline the greater problems of acclimatisation associated with eastward flights, the possibly unrelated disturbance of pituitary-adrenal function, and the major contribution of sleep disturbance to the jet-lag effect. Whether or not disruption of the melatonin secretory rhythm plays a part in the psycho-

logical disturbance of jet lag is unknown. The surprising symmetry of the rate of adaptation of melatonin to either eastward or westward flight requires further investigation, but it may be related to the overall photoperiodic control of its secretion and the strength of entrainment by natural light. One further comment may be pertinent: volunteers for such experimental studies are for a short period the centre of attention and so may be untypical. Another feature of the study by Désir and co-workers[16 17] was that it included a period of tourist activity between the two flights. It would be surprising if the eastward flight home, to normal concerns and problems, was not accompanied by a degree of depression unrelated to jet lag. In patients with psychiatric illness depression after a camping holiday has been described as a lethal possibility.[21]

Anticipation of jet lag and its prevention by planned manipulation of circadian rhythmicity before departure is possible using particular food-intake protocols, but for most people such an approach is impracticable.[1] Pharmacological manipulation of circadian rhythms poses even greater problems. Compounds including oestradiol, testosterone, theophylline, lithium, and tricyclic antidepressants[22] affect the length of the period of circadian rhythms in animals, but there have been few, if any, studies of their effects on human rhythms. Temporary discomfort is surely preferable to such medication.

Recommendations for passengers by the Advisory Group for Aerospace Research and Development[23] include the use of short-acting hypnotics during transmeridional flights to lessen the effects of jet lag. Subsequently an extended night's sleep, together with exposure to local social cues, is essential for rapid resynchronisation. Aircrew were recommended to keep sleep deficit to a minimum, remain on home-base time, and return rapidly to base. The practical application of such recommendations clearly presents difficulties, with particular reference to remaining on home-base time. Various formulae have been devised for calculating the rest-times necessary to achieve resynchronisation, depending on the number of time-zones crossed, flight duration, times of departure and arrival, and direction of flight, as well as the individual's age.[24]

Evolution may well solve the problem of jet lag before science. Laboratory animals, for example, become progressively less susceptible to some environmental cues, and normal healthy human beings are refractory, at least in part, to some of the major zeitgebers of the animal kingdom. Air hostesses in whom menstrual cycles are disturbed may stabilise after prolonged exposure to time-zone shifts.[11] Presumably, with sufficient exposure, we might all become more adaptable to rapid change of the external clocks.

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