

SHIFT WORK AND THE JET-LAG SYNDROME:
CONFLICTS BETWEEN ENVIRONMENTAL AND BODY TIME

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In today's highly industrialized societies, we are frequently exposed to acute time shifts of our 24 hour daytime schedule. Since World War II, many nations have introduced shift-work as an effective way to increase industrial productivity. In the United States, for example, it is estimated that 16% of all workers are on some form of shift-work schedule (Hedges & Sekscenski, 1979). Millions more individuals around the world subject their bodies to sudden shifts in time zones by the rapid travel made possible by the jet age. These changes in the nature of man's temporal environment have occurred over the last 40 or 50 years--a mere instant on the evolutionary time scale when compared to several million years of exposure to only the regular 24 hour period of the earth's rotation. We are discovering that humans have consequently developed a physiological apparatus which cannot always satisfactorily meet the demands imposed by external time shifts.

During the last 20 years, a considerable body of knowledge has accumulated on the circadian timing system which schedules man's body functions. Many physiological variables show oscillations, called "circadian rhythms", which are normally synchronized to the 24 hour external environment and persist with an approximately 24 hour period in environments without time cues (Halberg, 1960). Each is the product of the circadian timekeeping system within the organism (Pittendrigh, 1974) which enables animals to predict the major daily changes in environmental conditions which occur as a result of the 24 hour periodicity of the earth's rotation. Thus adaptive physiological and behavioral responses which may take several hours to be activated, can be initiated in advance of a predicted environmental challenge. The formal properties of the circadian timing system have been extensively described over the last 20 years (Aschoff, 1960; Bruce, 1960); however, relatively little is known about the physiological basis for circadian time measurement. Moreover, we are just now beginning to understand the role that this timekeeping system plays in a variety of pathophysiological conditions, including some induced by these acute time zone shifts of shift-work and jet-lag.

Varied degrees of stress may be imposed by different schedules. An individual flying from one time zone to another is exposed to a single acute shift in external time and may have ample time to adjust to the new schedule. A more complex challenge to the body's timing system may occur with rotation

shifts where the individual works a few days on each shift and thus is exposed to regular, repeated shifts in external time. The most demanding challenge, however, is a random work shift schedule where work time and time available for sleep bear no relation to the previous or subsequent days. Figure 1 presents the record of sleep time, work schedule and eating times of two airline pilots plotted against their normal 24 hour home time. As can be seen, the work, sleep, and eating schedules vary rather randomly when compared with the individual's home time, and all three of these variables occur with different time relationships to each other throughout the course of the records.

Unfortunately, current pilot duty schedules such as these are designed irrespective of body time, and are governed by FAA regulations in which rest time is computed solely on the basis of accumulated duty time with no account taken of the individual's circadian or body time. Such schedules create a conflict of external timing information with the internal time of the individual. The external time of the environment, as created by work demands, is rapidly and randomly shifted on a day to day basis from the individual's home time. At the same time, the individual's meal timing, which may constitute another environmental input influencing body time, is also shifted but not always to the same degree as the work schedule. Finally, the social time frame of the individual's life at home, interspersed with his schedule as off-duty days, remains fixed to his domicile time. As a result, as one can see from the sleep records of the pilots, they fail to adapt to any particular fixed schedule.

Three factors appear to underlie the body's response to these timing conflicts. We will refer to as Factor 1 the fatigue and/or sleep-loss directly consequent to the travel or start of a new shift, which are independent of the timing conflicts. For example, flying from north to south does not result in a time zone shift; however, the actual stress of the flight itself will influence the individual's performance.

The other two factors are a result of the shift between external and internal time. Factor 2 is the direct effect of the disparity between external and internal body time. For example, an individual's minimum daily performance capability may be at 4:00 am, the time of day when there are normally no external challenges. However, after a flight across six time zones to Europe (a phase advance of six hours) the circadian timing system takes several days to resynchronize. Before it starts to adjust, the person's body time will be at 4:00 am but local environmental time may be 10:00 am, a time of day when the individual may be expected to operate with maximum effectiveness at an important business meeting or combating rush-hour traffic.

Factor 3 is more subtle. Because the circadian timing system is composed of several separate oscillators or "clocks", and each resets at a different rate to the new environmental time, there are timing conflicts between the rhythmic functions of the various physiological systems which further reduce the individual's optimum abilities.

Studies in a Primate Model

To study the factors described above it is necessary to perform precisely controlled experiments in which the individual contributions of each factor

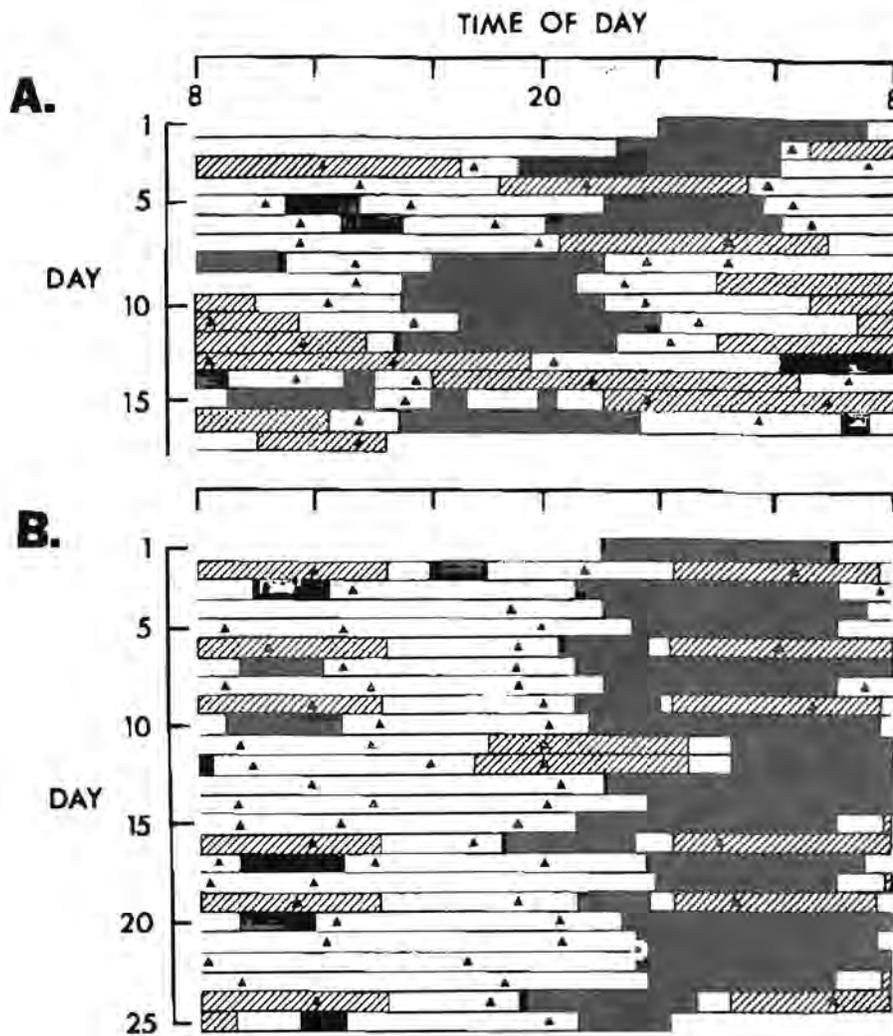


Figure 1. This figure depicts the sleep (■), eating (▲), and work (▨) schedules of two commercial pilots over a series of consecutive days. Each 24 hour day is successively plotted underneath the previous starting with day 1 on top. The time of day (indicated at the top) begins on the left with 0800 in the morning of the pilot's home time. As can be seen, the work schedule imposed on the pilot and the resulting rest and eating schedules do not fall into any coherent pattern but instead are relatively random throughout the period depicted.

can be isolated, measured, and analyzed. To do this one must both control the environment and monitor all the various biological functions continuously. Because of the severe limitations imposed by doing such rigorous research in man, we have utilized a non-human primate model, the squirrel monkey (*Saimiri sciureus*), a small (approximately 1 kilogram), day-active, South American animal. Using these animals we have investigated a series of questions regarding the influences of Factors 2 and 3 in shift-work and jet-lag and their resulting implications for physiological regulation. We will not be discussing here in great detail the potential implications of Factor 1 as they have been discussed widely elsewhere and are a generally recognized contributory factor (Aldama, 1977; Day, 1976; Grandjean, 1968).

Effects of a Single Environmental Time Shift

Using this animal model we first examined the effects of a single phase-shift of the light-dark (LD) cycle (Moore-Ede, Kass, & Herd, 1977). The rhythmic patterns of seven different physiological and behavioral variables are shown in Figure 2A. Plotted at the bottom of the graph is the light-dark cycle to which the animal is subjected. As indicated, the animals were in a 24 hour light-dark cycle with lights off from 2000 to 0800 each day and the lights on from 0800 to 2000. The cycle thus consisted of 12 hours of light and 12 hours of dark (LD 12:12). During the second day the animals were subjected to the equivalent of an 8 hour phase shift in time zone. An additional 8 hours of light were added from 2000 to 0400 following which the lights were turned off and the LD 12:12 cycle was reinstated at this new phase (lights on from 1600 to 0400 hours each day) for the rest of the experiment. Before LD phase-shift all of the variables were rhythmic with 24 hour periods. After the phase-shift, each of the rhythms moved over to match the new phase of the LD cycle but not immediately or at the same rate. For example, the behavioral rhythms of feeding, drinking, and activity along with the body temperature rhythm moved over and resynchronized at a faster rate than the urinary excretion rhythms.

The average rate of resynchronization for each of these variables (for a group of four different animals) is shown in Figure 2B. Plotted here is the time of occurrence of two phase markers (the time the rhythms moved upwards and downwards through their average value) from each successive cycle of each animal. Before the 8 hour phase-shift it can be seen that the phase of each rhythm occurs at approximately the same time each day as indicated by the minimum deviation of the time of occurrence of the phase points from the phase scale on the abscissa. After the 8 hour LD phase-shift all of the phase markers began to move over to the new LD phase which was -8 hours displaced. However, some variables moved over faster than others. To clarify the rate of shift, an exponential curve has been fitted to each set of data. As indicated in Figure 2 the activity feeding and drinking rhythms were all essentially resynchronized to the new light-dark cycle within 48 hours. The temperature rhythm took approximately 24 hours longer to resynchronize. The urinary potassium, sodium, and volume rhythms on the other hand took approximately 7 days to completely resynchronize. Similar results have been found in man (Wever, 1979). Thus, when an individual is exposed to an abrupt shift in the light-dark cycle he does not become completely resynchronized with the new environmental time for at least a week. Additionally, since resynchronization is occurring in some variables at a faster rate than others, a phenomenon of in-

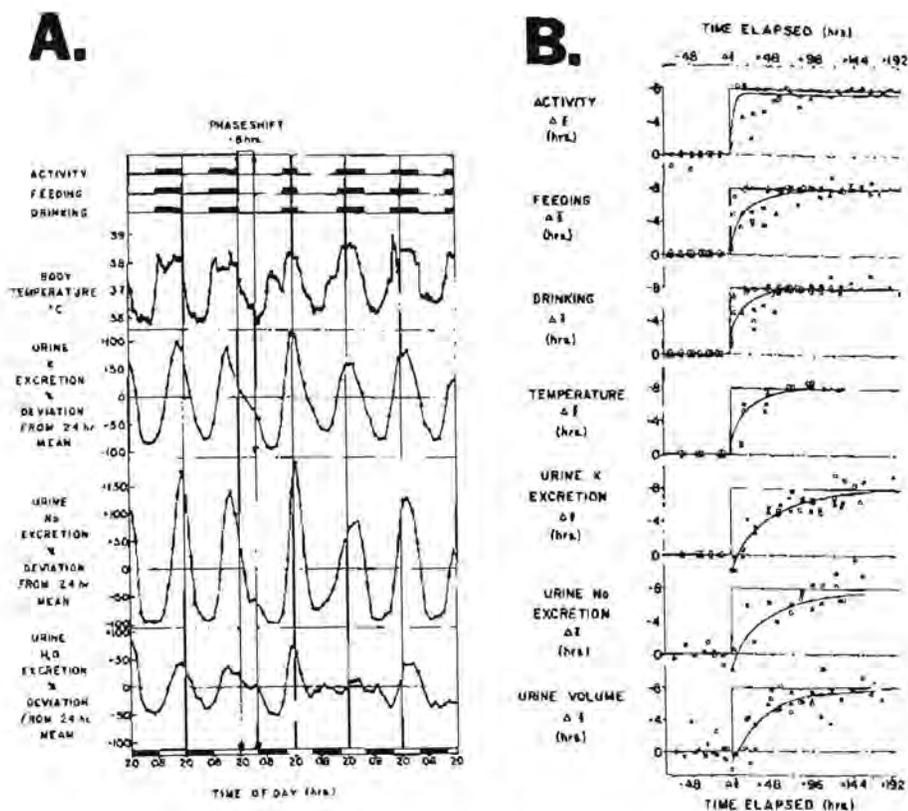


Figure 2. Response of a monkey to an 8-hour phase-delay of the light-dark cycle. Plotted in A are the circadian rhythms of activity, feeding, drinking, body temperature, and urinary potassium, sodium, and water excretion during 2 control days with the lights on from 0800 to 2000 hours, and then for the first 4 days after a light-dark cycle phase-shift where lights were now on from 1600 to 0400 hours daily. Each circadian rhythm gradually resynchronized with a new light-dark cycle phase. In B the changes in phase of 2 phase markers on each successive cycle, of a group of 4 animals, as compared to the phase of the same markers during control days, were plotted as a function of time elapsed after light-dark cycle phase shift. An exponential function was fitted to the phase shift of the rhythm markers. Circadian rhythms of activity, feeding, drinking, and body temperature phase-shifted significantly ($p < .05$) more rapidly than urinary rhythms to the new light-dark cycle phase.

ternal desynchronization between the various rhythmic variables is observed. As a result, after a phase-shift, individuals are externally desynchronized from the environment (Factor 2) due to the drag from the internal timekeeping mechanism and internally desynchronized (Factor 3) because of the different rates of resynchronization of the components of this timekeeping mechanism.

Factor 3, internal desynchronization, particularly becomes a problem when there are no time cues in the environment. In this rather unnatural state the organism is said to be "free-running" and expressing its own internal circadian period via its endogenous timekeeping system. The circadian timekeeping system of mammals is composed of a group of potentially independent oscillators, which are normally coupled to one another as well as being synchronized with the external environment (Moore-Ede & Sulzman, 1977; Pittendrigh, 1974). However, occasionally, these oscillators can be separated by internal desynchronization and free-run with different periods since the internal coupling mechanisms are not always sufficient to maintain appropriate synchronization between the rhythms. We have previously demonstrated internal desynchronization between the circadian rhythms of body temperature and urinary potassium excretion in squirrel monkeys maintained in constant environmental conditions (Sulzman, Fuller, & Moore-Ede, 1977a), and Aschoff and co-workers (Aschoff, 1965; Aschoff, Gerecke, & Wever, 1967; Wever, 1979) have demonstrated internal desynchronization between the circadian rhythms of activity and body temperature in man. Even when internal desynchronization is not seen, some change in internal phase angle relationships between different rhythms is found when animals are placed in environments free of time cues (Kreibel, 1971; Mills, Minors, & Waterhouse, 1977).

Several different elements of the environment are capable of providing temporal information to an individual. In addition to light-dark cycles, we have previously shown that one of the key elements in the environment which can affect the timing of an organism is the rhythmic availability of food (Sulzman, Fuller, & Moore-Ede, 1977b). That is, when monkeys were allowed access to food for 3 hours a day at the same time of day, and fasted the other 21 hours (eating-fasting; EF 3:21), they become synchronized to the 24 hour cycle even in the absence of any light-dark cycle. However, we have also shown that these environmental synchronizers do not couple all of the oscillators in the organism in the same manner (Sulzman, Fuller, Hiles, & Moore-Ede, 1978). For example, Figure 3 shows the differential coupling which can occur when a monkey is exposed to conflicting zeitgebers (a situation which is analogous to some shift schedules). Here the rhythms of drinking, colonic temperature, urinary potassium, and urinary volume are averaged from several cycles of a group of 4 animals. All of the animals were exposed to a normal LD 12:12 cycle as indicated in the drawing. However, these animals were at the same time exposed to an EF cycle at two different times of day. The animals on the left were allowed access to food for the first 3 hours of lights on from 0800 to 1100 in the morning while the animals on the right were allowed food only from 1600 to 1900 in the evening before lights out. Figure 3 shows that the drinking and urinary volume and potassium rhythms moved their phases to match the phase of the EF 3:21 cycle, while the timing of the temperature rhythm was not affected by the different EF schedules and kept the same phase relationship to the LD cycle. This indicates that although both environmental variables supply temporal information to the organism, they do not affect all rhythms in the same way and thus create a disparity in phase

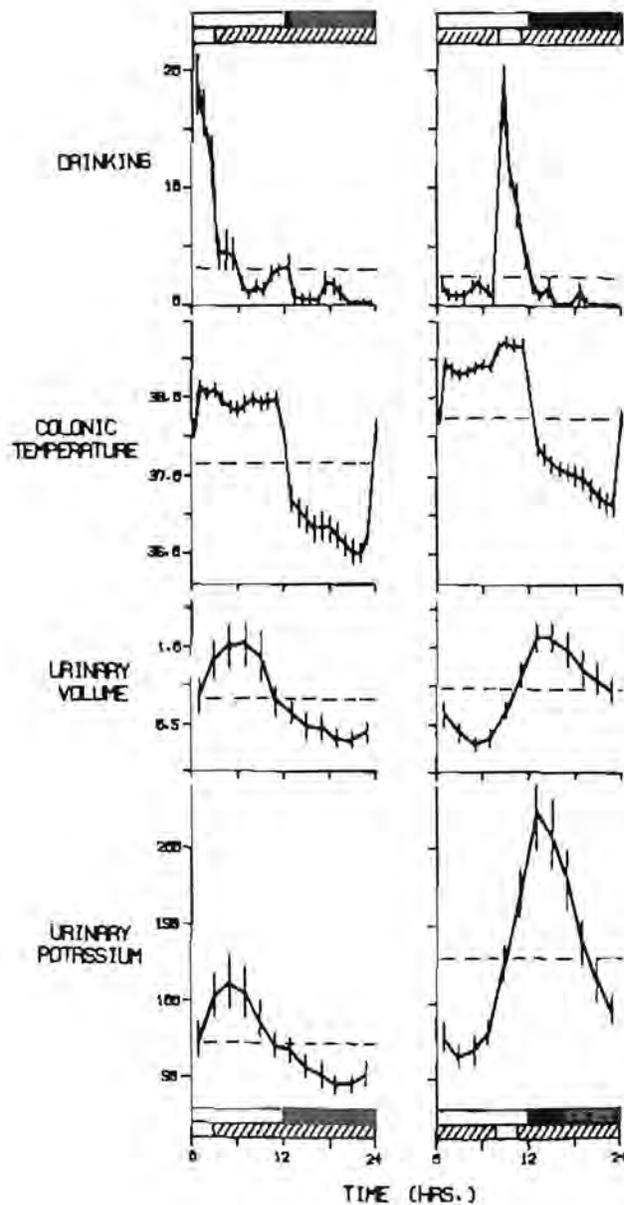


Figure 3. Average waveforms of rhythms of drinking, colonic temperature, urinary volume, and urinary potassium (mean \pm S.E.) of a group of 4 monkeys concurrently entrained to an LD 12:12 and EF 3:21 cycle. Lights were on from 0 to 12 hours and off from 12 to 24 hours. Animals on the left had food available from 0 to 3 hours and animals on the right had food available from 8 to 11 hours. Drinking is plotted in mls of water consumed per hour, colonic temperature in degrees centigrade, urine volume in mls per hour, and urinary potassium in microequivalents per hour. From 24 to 26 cycles of data were used to calculate each waveform. As can be seen, the timing of the temperature rhythm was not affected while the other rhythms were phase-shifted by the EF cycle.

angle between these variables. In addition to applying multiple synchronizers with conflicting phases, it can also be shown that applying the synchronizers with conflicting periods can have a similar effect in producing internal desynchronization (Sulzman et al., 1978). The message for the shift workers is that disorders of internal timing (Factor 3) may occur if some time cues shift, such as the LD cycle; but others, such as the timing of meals, do not.

Effects of Repeatedly Shifting Schedules

There are many more extreme examples of external time shifts than the single shift in one environmental parameter that we have just described. For example, rotating shift schedules exist where an individual may be rotated through a successively later shift every week. Thus, the individual never becomes totally acclimated to the shift he is on. If the sequence of shift time changes daily the average effect is that the individual will not be working on a 24 hour day, but instead on one that has a day length significantly different from 24 hours. Enlisted men in U.S. Navy submarine crews are typically assigned work schedules with an 18 hour day-night cycle. This constitutes a phase shift of 6 hours on each successive day for the individual compared to his normal 24 hour time. However, one of the key properties of the circadian timekeeping system is that circadian oscillators are only capable of synchronizing to environmental cycles with periods close to 24 hours (Enright, 1965; Mills et al., 1977; Wever, 1979). This phenomenon, known as range of entrainment, means that the primates and man will free-run when exposed to environmental synchronizers with periods outside the range of approximately 22 to 26 hours. Thus, when an individual is exposed to an 18 hour day, his body time cannot synchronize to this period but rather reverts to a free-running behavior determined by his internal timekeeping system. This is a far from optimum state and the individual will consistently be out of synchrony with the demands of his environment.

The picture is complicated further because the environment has a direct influence on the expression of the various rhythms. An example of this type of direct environmental influence is seen in Figure 4. Here a monkey is exposed to an 18 hour day (LD 9:9). Figure 4A shows the resultant body temperature levels of the monkey during 5 successive LD 9:9 cycles. What can be seen is a relatively complex rhythmic behavior resulting from two different sources. The first component is a circadian rhythm free-running with an approximate 24 hour period since an 18 hour period is outside the monkey's range of entrainment. When the circadian phase of each successive 24 hour cycle is computed mathematically and plotted as a time of day occurrence as shown in Figure 4B, one can see the maximum is occurring with consistently different relationships to the LD cycle. On Day 1 the maximum occurs during the lights on; on Day 2 the maximum occurs after lights off; on Day 3 the maximum occurs just after lights on; and on Day 4 the maximum occurs about the same time as it did on Day 1. This circadian component is thus showing 4 cycles superimposed on the 5 18-hour LD cycles. Simultaneously, however, we are seeing a direct influence of the light (and dark) on the body temperature rhythm such that when the lights are on, the body temperature is higher than when the lights are off.

To show both of these rhythmic components (the free-running circadian components generated from the endogenous timekeeping mechanism and the pas-

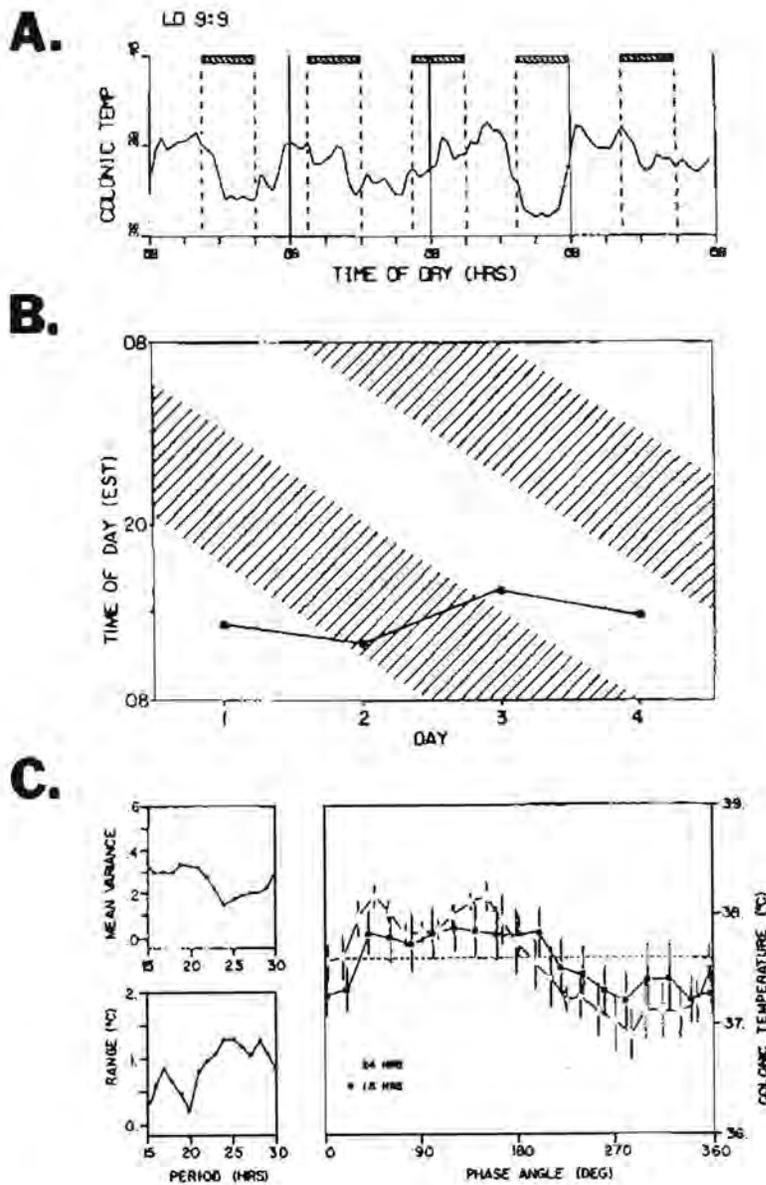


Figure 4. Plotted in A is the colonic temperature response of a monkey exposed to an 18-hour light-dark cycle (LD 9:9). The phase plot in B indicates that a circadian rhythm of body temperature (shown by the phase points) is persisting with a free-running period independent of the 18-hour light-dark cycle, (indicated by the clear areas for the light and the hatched areas for the dark). Autocorrelation analysis of the data in C shows both by the mean variance and range maximum plots over a period range of 15-30 hours that there is no clear indication of any single periodicity in the data; rather there is an indication of periodicity at around 18 hours and again at about 24. When the 24 hour and 18 hour averaged rhythms are simultaneously plotted we see that a significant rhythm at both of these frequencies is occurring.

sively driven 18 hour component by the imposed environmental light-dark cycle) we have performed the autocorrelation analysis of the body temperature pattern in Figure 4C. This analysis shows minimum mean variances and maximum ranges occurring at 18 and 24 hours. Thus, both of these calculations indicate that there are rhythmic components in this body temperature data with these two periods. To quantify these influences we have plotted on the right in Figure 4C the average waveforms in the body temperature data at periods of 18 hours and 24 hours. The internally timed component (the 24-hour cycle) shows the largest amplitude, but there is still a significant rhythm occurring at the 18 hour period as a result of the concurrent LD cycle. Thus, from these types of studies we recognize two conclusions can be drawn. The first is that a range of entrainment phenomenon exists and must be taken into account for rapidly repeating shift work schedules. Second, besides the active synchronization of the biological rhythms these external time cues can have direct passive influences on the rhythms themselves (Aschoff, Klotter, & Wever, 1965).

To further investigate these passive influences of light-dark cycles on the body temperature rhythm of the squirrel monkey we have examined the extreme case of exposing a group of monkeys to 4 hour light-dark cycles (LD 2:2). As is shown in Figure 5, when the body temperature rhythm of the animals in the LD 2:2 cycle was compared with the same group of animals exposed to an LD 12:12 cycle it was found that the light intensity had two specific influences on body temperature regulation. First, when the lights were off the body temperature was always lower than when the lights were on. Second, there was a circadian variation in this passive response in that the light intensity had a greater effect in changing body temperature during the night than it did during the day. Thus, body temperatures comparing lights on and off during the day were different by only a few tenths of a degree centigrade while this difference was over 1 C during the night. We have also found that these light intensity effects were present when the animal was free-running in constant light. Under these conditions, the body temperature rhythm amplitude and mean level was a direct function of light intensity.

Pathophysiological Implications

As of this date we do not know the answer to the question whether shift-work or jet-lag have life-threatening or otherwise major health impact in humans. No rigorously controlled long-term follow-ups on a large population of shift workers have been performed. Data on other organisms, however, do exist which indicate that Factors 2 and 3 may play a significant role in some health problems. For example, Aschoff et al. (1971) have shown that flies exposed to continuously shifting LD schedules have shortened life spans as compared with flies in a 24 hour LD cycle throughout their life. Halberg has extended these findings to mice (Halberg & Nelson, 1976). Moreover, organisms exposed to light-dark cycles which are outside the circadian range of entrainment also display shorter life spans than animals within the circadian range (Pittendrigh & Minis, 1972).

Regulation of behavioral and physiological functions within primates and man have, however, been shown to be susceptible to effects of timing disparity. For example, we have shown that when circadian synchronizing cues are removed from the environment, temperature regulation in the squirrel monkey is markedly impaired (Fuller, Sulzman, & Moore-Ede, 1978) as is seen in Figure 6. Animals

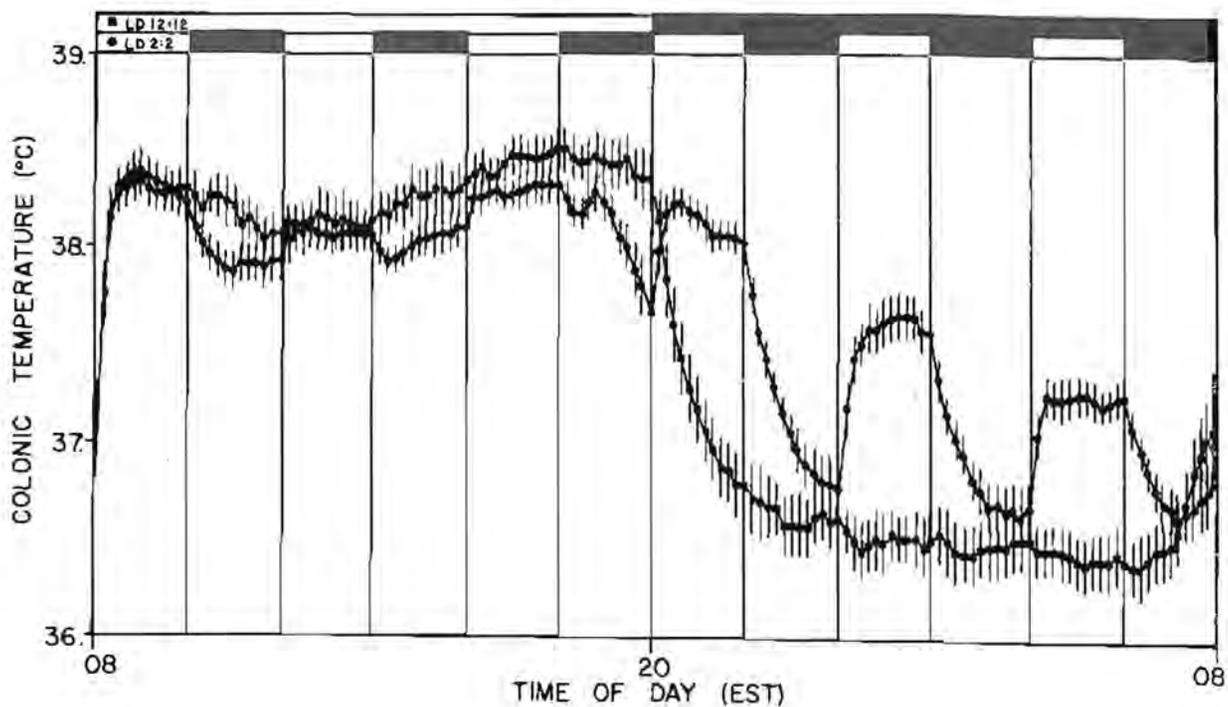


Figure 5. Plotted here are the average body temperature waveforms of a group of 4 monkeys initially exposed to an LD 12:12 cycle followed by an LD 2:2 cycle. The passive effects of light on the regulation of body temperature can be seen by comparing the superimposed curves with each other. The temperature was sampled every 10 minutes and plotted are the means (\pm S.E.) of approximately 10 cycles from each light regime. As can be seen the body temperature is always lower when the lights are off and the greatest effect of light is observed during the animals night.

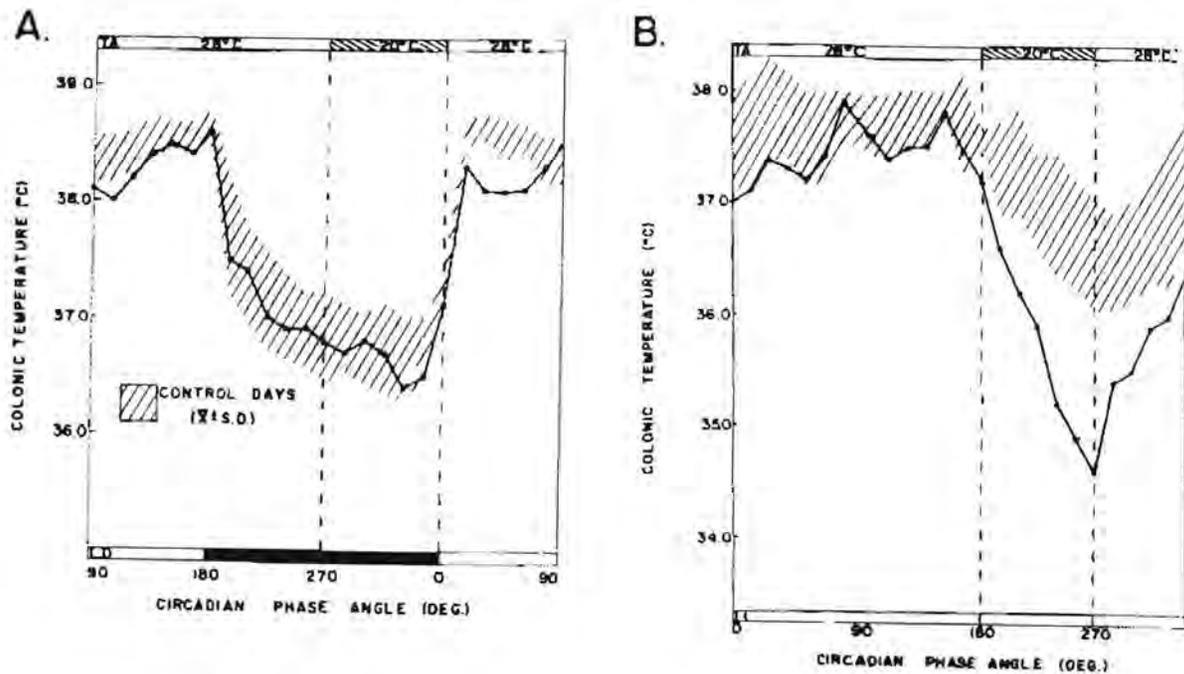


Figure 6. The effects of 6 hour cold exposures on body temperature in a monkey entrained to an LD 12:12 cycle in A and a monkey free-running in constant light in B. At the top of each graph the ambient temperature is indicated on the day the cold exposure was instituted; light conditions are indicated on the bottom of each graph. Since the periods of the rhythms were different in the 2 lighting conditions (that is, 24 hours in A and 25 hours in B), the data were normalized so that each cycle was set equal to 360. The shaded area represents the mean (\pm S.D.) of the previous 3 cycles (ambient temperature equals 28°C). As can be seen the animal in light-dark cycle showed very little effect of the cold exposure, maintaining its body temperature in the shaded region while the animal in constant light showed a major inability to maintain body temperature during the cold exposure.

synchronized to the environmental time cues are able to maintain body temperature without difficulty during cold exposure. An example of this can be seen in Figure 6A where an animal is exposed to an 8 °C drop in ambient temperature during the night. The body temperature is maintained at the previous control levels (shaded rhythmic area) throughout the cold exposure. In contrast, Figure 6B, shows that when circadian synchronizing cues are removed from the environment some monkeys cannot maintain body temperature when exposed to this same mild cold stress. That these results are not a direct consequence of isolation of the animal of constant light *per se* has been shown in monkeys synchronized to a 24 hour period by EF cycles in constant light (Fuller, Sulzman, & Moore-Ede, 1979). These animals were able to defend body temperatures during similar cold exposures. Finally, another group of animals, in which forced internal desynchronization was consistently produced, showed an inability to maintain body temperature during cold exposure. Yet, when these same animals were synchronized to a light-dark cycle they were quite capable of maintaining body temperature (Fuller et al., 1979). The results of these studies indicate that effective thermoregulation requires the proper temporal synchronization of the various physiological systems responsible for the maintenance of body temperature.

A large body of literature exists which indicates that psychomotor performance of both primates (Rohles & Ptacek, 1973) and man is less than optimal during rapid phase shifts of the external environment. For example, Nicholson (1973) has shown that pilots exposed to shift schedules such as those in Figure 1 may suffer an increase in physiological tremors after many successive shifts in body time. Klein, et al. (1970) have also confirmed that acute shifts across time-zones lead to decrements in pilot performance.

Thus, while major health and longevity problems have not been directly implicated with shift work schedules or jet-lag *per se*, the potential does exist for problems to occur. Decreases in behavioral and physiological performance can be documented as a result of conflicts between environmental and body time. Further, the combination of these individual deficits which are just now being recognized may contribute to more subtle changes which may result in long term health problems yet to be identified.

Conclusions and Recommendations

As we have discussed, there are a number of implications for human health of the shift-work schedules or the acute time zone shifts seen with jet travel. We have no final answers, yet we can suggest several tentative conclusions. It is apparent that further studies need to be performed both on animal models and man. These studies need to isolate Factors 1, 2, and 3, for individual study and in combination with each other in a rigorous manner. We need further to characterize the structure and function of the human circadian timekeeping system and determine its performance limitations. The environmental parameters which have direct influences on man must also be isolated to determine both their active and passive effects on each of the various physiological systems. Finally, we need to develop effective therapeutic techniques to aid in the readjustment to new schedules.

Even though no final answers exist, several recommendations could be made at this time to help individuals who must endure these types of schedules.

The first would be to minimize Factor 1: the fatigue factor or sleep loss. Sleep is beneficial and should be optimized whenever possible. This may mean for a traveller, whenever practical, choosing a daytime flight which does not impinge on the sleep period of either home or visiting time zone. Unfortunately, transatlantic flights are largely at night taking more into consideration the expediencies of maximizing aircraft use than the health and comfort of the passengers and crew. Secondly, because of the potential conflicting nature of time cues from the environment, it would be helpful whenever feasible to shift all environmental parameters maximally so that even though an individual is working at a new shift schedule, or is in a new time zone, his entire temporal environment (i.e., social, lighting, temperature, food timing, etc.) is synchronized in such a way that it presents a single unified 24 hour environment for the body. This will help the individual resynchronize to the environment and maintain that synchrony. Finally, if a shift is required for only a relatively short period of time (i.e., one or two days), the individual is better off not attempting to shift at all but maintaining himself as much as possible on his own time. Thus, he would already be synchronized to his domicile time when he returns.

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ON VARIATIONS IN WORK-SLEEP SCHEDULES

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