

STUDIES IN HUMAN SLEEP¹

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We shall here outline two special interests that we and our colleagues at Edinburgh have had: in the pharmacology of sleep and the function of sleep.

When examining the effects of drugs on the human brain by studying their action on sleep, it is important to conduct the work during many weeks. Single-dose experiments can be misleading. Most psychotropic drugs are taken for long periods of time and should therefore be studied for long periods. In most of our work we today use people in the age group 40-70 who regard themselves as poor sleepers. There are usually first two or three nights in the laboratory, to become accustomed to the conditions. After this there comes a series of nights establishing a baseline for the individual. Throughout all this period they will have been receiving blank pills but now will start on genuine ones and the first few nights while they receive the active drug will be recorded, as well as further nights at intervals over the subsequent weeks or months. If there is a gap of more than a few days between a group of recordings then at least one more night for adaptation in the laboratory is needed at the start of each group of nights. Finally the subjects will receive again blank pills and their sleep will be recorded again during the early withdrawal period and at intervals during the next three to eight weeks. In this way can be assessed the immediate effects of the drug, cumulative effects, tolerance manifestations, withdrawal abnormalities and the time needed for withdrawal abnormalities to subside (35).

When the recording work of the experiment has been completed the all-night records are coded, are then scored "blind" in terms of the customary international criteria, using epochs of 20 s duration. The raw

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data so obtained are later analysed by computer. Among the many easily-measured variables is paradoxical or REM sleep, and Fig. 1 illustrates how this measure can demonstrate that many weeks are needed for the

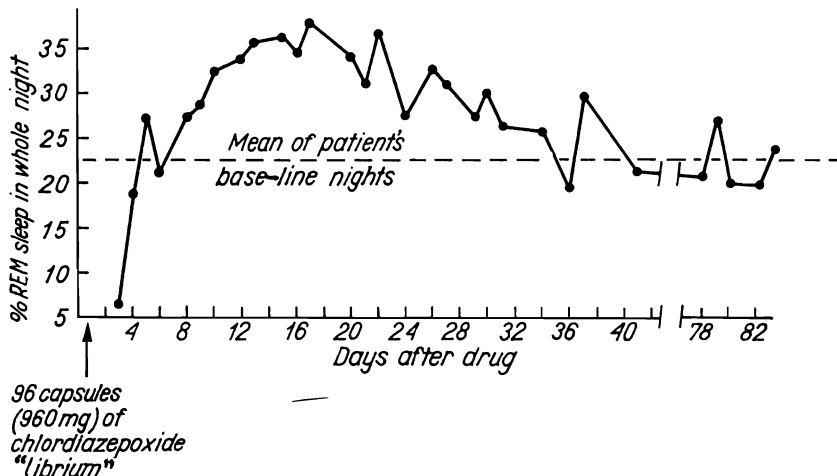


Fig. 1. Paradoxical (REM) sleep after chlordiazepoxide overdose in woman of 20. Six weeks "repair". (From Oswald et al. 34).

brain to recover after a single large dose of chlordiazepoxide. In addition one may look at the durations of all the other different stages of sleep throughout the night, but it is equally valuable to look at the frequency of transitions between stages and at the distribution of events, hour by hour, throughout the night.

We are also interested in the effects of drugs on the endocrine system. A small catheter is inserted into a forearm vein and connected to a flexible extension that passes through the bedroom wall so that while the subject sleeps blood can be sucked away. In the intervals the catheter system is kept filled with heparinized saline. Fig. 2 is based upon half-hourly sampling of blood from eight men, and depicts the integrated plasma levels of corticosteroids for the period 2400-0630 h. The sampling was done solely during sleep. Initially each subject had two nights sleeping in the laboratory in order to adapt to the catheter. The four subsequent baseline nights are depicted in Fig. 2. When the daily pills change from placebos to a modern anti-anxiety drug there is a fall in the plasma corticosteroids (significant on analysis of variance) and then a significant rise above baseline in the early withdrawal period with finally a return to baseline. It would appear that an anxiety-relieving drug can be associated with lower indices of "stress", but that when it

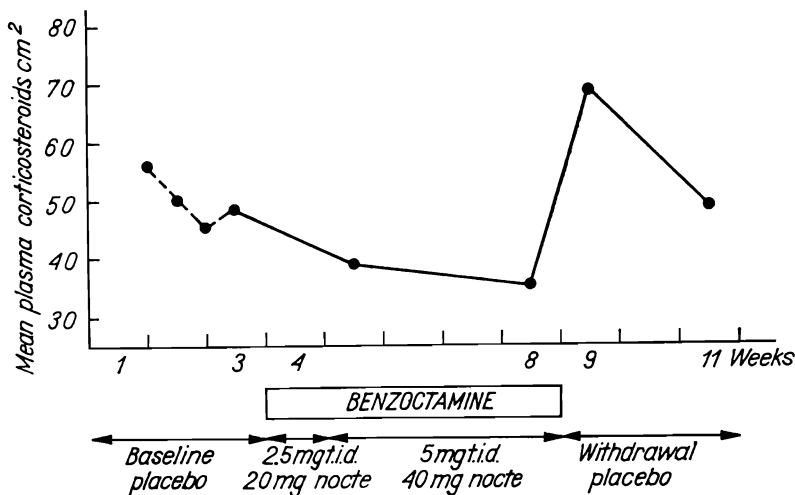


Fig. 2. Integrated whole-night plasma corticosteroids, means for 8 men. (Data from Ogunremi et al. 31).

is withdrawn a “stress” reaction is present in the endocrine system even during sleep.

It may be of interest to recall that after the withdrawal of such drugs subjects frequently describe nightmares and in the early withdrawal period there is usually an increase of daytime anxiety above baseline levels. Most such agents reduce the amount of REM sleep and there is a rebound increase above normal of this too after withdrawal.

The function of sleep

Among the blood contents in which we are interested is growth hormone. The Japanese discovery that growth hormone is secreted in large amounts during sleep (22, 46), during slow-wave sleep in particular (40), gave rise to a new interest in the function that sleep may have for growth and restoration. It had been known that growth hormone increases the rate of synthesis of protein (27). Some years ago one of us was prompted to write of slow-wave sleep (NREM) that “its chief function is for bodily restitution, while REM sleep may be chiefly for brain repair” (32). These ideas were later developed (33, 36) and now Hartmann (19) and Stern and Morgane (45) have put forward the same general ideas but each proposes that REM sleep has a particular role for restoring cerebral catecholamine mechanisms.

In complex organisms, metabolism is organised in such a way that during a period without food the energy needs are principally furnished

by depleting fat and glycogen stores. Nevertheless, amino acids can be and are burned to supply some of the energy when requirements are more intense. A higher metabolic rate (as in waking activity) increases the biologically-wasteful utilization of these protein building-materials, simply as an energy source. On the other hand, when energy requirements are low (and metabolic rate falls lowest in sleep) then these requirements are more easily matched by fuel stores and hence catabolism of amino acids is reduced.

These facts imply that a relative enhancement of net protein synthesis would be inevitable at times when two conditions prevailed; when food stores had been replenished and when metabolic rate was low. These two conditions are, of course, found during the rest period of sleep that follows the active, food-gathering period of wakefulness.

In higher animals, sleep has evolved as an active process, mediated by the central nervous system. Although, as earlier stressed, biosynthetic activity would inevitably be greater during the rest period, the central nervous system control, whereby inactivity is ensured, has further strengthened the association between rest and synthetic activity, so that in Man there are, for example, at least four sleep-dependent anabolic hormones. Thus in Man, sleep brings about the release of growth hormone which promotes protein synthesis, but the hormone also mobilises fat stored up by day, which further ensures that protein will not be burned as an energy source during sleep. In the night, corticosteroids are low, as determined by a circadian rhythm governed by the central nervous system. The metabolic actions of corticosteroids are antagonistic to those enhanced by growth hormone. In the night when corticosteroids are low the growth hormone that is secreted in sleep is consequently even more effective in stimulating protein synthesis.

It is, therefore, apparent that a combination of lower metabolic rate, and less protein degradation, together with the special pattern of hormone secretion, effectively ensure a higher rate of net protein synthesis during sleep.

Cell division is an important synthetic activity for growth and restoration. Peaks of mitotic activity occur in human bone marrow and in human skin soon after the usual onset of sleep (9, 15, 25, 29). Cellular division in the skin of rodents (17, 18, 39), and in their bone marrow (8) are maximal during the hours when the animals are predominantly asleep. If this is true for other systems it would seem consistent with the recent knowledge that there are four important hormones, all concerned with the regulation of tissue growth and development in man and dependent upon sleep.

When a hormone is present in greater amounts during sleep it

does not necessarily mean that it is sleep-dependent. Corticosteroids, for example, rise during the later part of sleep but they do so whether the individual is awake or asleep, as a manifestation of a circadian rhythm and not because the rise is sleep-dependent. Sleep-dependent hormones are those that can be shown to be secreted in large amounts during sleep at the normal time, but not if the person stays awake. They are, however, secreted if he sleeps 12 h later than the normal time. Human growth hormone is sleep-dependent and also requires the presence of slow-wave sleep stages 3 and 4 (41, 43). Also dependent on sleep but not closely linked with any EEG-defined stage are prolactin (42) and, in early puberty only, luteinizing hormone and testosterone (6, 7).

Several years ago we found that if it was a long time since sleep had last occurred then slow-wave sleep stages 3 and 4 had immediate priority, as if to help restoration (5). A special role for this kind of sleep in promoting restoration could be inferred from the report of Baekeland and Lasky (3) that when athletes had exercised hard during the day they got more slow-wave sleep at night, and from the report of Hobson (20) that when cats had been obliged to take extra physical exercise they too got a significant excess of subsequent slow sleep.

Other authors failed to confirm the finding of Baekeland and Lasky, though none of us had used athletes in order exactly to repeat their experiment. Shapiro et al. (1975) did so and confirmed the original claim. At Edinburgh, however, we found a significant increase of growth hormone during sleep in men who had taken strenuous exercise during the day compared with days when they had taken only an ordinary amount of exercise (1). On the nights when the anabolism-promoting growth hormone was increased the catabolism-promoting corticosteroids were reduced by a significant amount.

It might be said that exercise burns up the tissue reserves and this is something that can also be done by acute starvation. Under these circumstances there is an increase during sleep in the protein-conserving growth hormone in the blood (37). We have ourselves observed a significant increase in stages 3 and 4 sleep during acute starvation (24, 30).

Tissue reserves can also be burnt up fast by an excess of thyroid hormone. For some years it was known that hypothyroidism was associated with absence of stages 3 and 4 sleep and that these stages returned during thyroid treatment (23). We have reported greatly increased amounts of stages 3 and 4 sleep in hyperthyroid patients and have also some evidence of an increase in growth hormone secretion (12). Loss of tissue can also be induced by amphetamine derivatives and the one known as fenfluramine, in chronic administration, causes a large increase

of stages 3 and 4 sleep (28) and we have some evidence of increase of nocturnal growth hormone (11).

Even one additional hour of wakefulness in the middle of the night leads to a significant increase in the amount of stages 3 and 4 sleep and of plasma growth hormone in the remainder of the night (4). It is as if the extra wakefulness demanded extra amounts of sleep of high restorative value.

Paradoxical (REM) sleep and cerebral synthetic processes

Many authors have shown that cerebral blood flow during paradoxical sleep is considerably increased above the levels present during wakefulness (e.g. 47). Tissue blood flow is generally proportional to oxidative metabolism and obviously during sleep the brain is not working so strenuously in order to cope with the external environment, so it would seem as if the extra blood is required for needs within the brain, presumably of an anabolic nature. Such an idea would be in keeping with the report by Van den Noort and Brine (48) that brain ATP rises during the sleep of rats and with the finding that RNA synthesis in rabbit cortex increased as the sleep EEG became less synchronized (49). There is a high proportion of REM sleep or its equivalent in young animals at those times when there is rapid brain growth, whereas when the brain is shrinking through failure of synthetic processes in senility there is an associated decrease of paradoxical sleep (13). In mental defectives there is a relative deficiency of paradoxical sleep (14, 38); it is possible that mental defectives require less intense brain synthetic processes. A number of animal experimenters have claimed that extra learning tasks are associated with more REM sleep in animals and that lack of REM sleep impairs learning performance (e.g., 20). We were unable to confirm that massive learning in man, brought about by the wearing of distorting spectacles, caused any increase of REM sleep (2) but since most cerebral protein synthesis must be for the maintenance of existing tissue this is not really very surprising.

My colleagues and I have studied the sleep of many patients in the weeks following recovery from self-administered overdose of drugs. Under these circumstances there is no excess of slow-wave sleep but in these weeks, when the brain is presumably having to repair itself, there is usually a very large excess of paradoxical sleep, as Fig. 1 illustrates (16, 34).

In the Soviet Union Demin and Rubinskaya (10) have measured protein and RNA in cerebral neurones and found these to be decreased in association with deprivation of paradoxical sleep. One of their colleagues, Dr. A. Panov, has repeated the work and confirmed that this

is so even when the paradoxical sleep deprivation procedure is brief and insufficient to cause any corticosteroid evidence of a stress reaction. In Rostov-on-Don Kogan et al. (26) have been able to determine the rate of protein synthesis in small cerebral biopses in relation to the stages of sleep of the cat, and find a 30% reduction below waking levels during slow-wave sleep, and a rise of about 7% above waking levels during paradoxical sleep.

It would therefore seem that today there is a good deal of evidence that paradoxical sleep is a time when it is possible (though not obligatory) for certain synthetic processes in the brain to be increased above waking levels. There would seem to be other good evidence that sleep in general, and slow-wave sleep in particular, is associated with more general bodily synthetic functions. Further support is lent to this by the study by Zepelin and Rechtschaffen (50) who, in a survey of 29 species, found a high positive correlation between metabolic rate and the daily duration of sleep.

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