No. 61
Published April 1997

Karger Gazette

Sleep

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The Phenomena of Sleep

Human sleep seems to have much in common with that of other mammals. It occurs regularly each day, largely under the influence of the 24-hour circadian rhythm. There is a typical body posture, a specific place to sleep, other behaviors and physical activity cease, the eyes close, and there is a generalized reduction in sensory awareness. The organ showing the clearest changes during sleep compared with relaxed wakefulness is the brain. This is particularly obvious in the electroencephalogram (EEG), which demonstrates the electrical activity of the brain. Focussing on the brain in this way is appropriate in other respects, as not only does the brain contain the control mechanisms of sleep, but of all the body's organs, it is the brain (especially the cerebral cortex) for which sleep seems to be the most vital. This is especially the case for those mammals with a more highly developed cerebral cortex, culminating in humans [1].

For many small mammals, such as rodents, sleep has other particular benefits, as it provides the only real opportunity for physical rest, and confines the animal to the thermal insulation of a nest. In these respects, sleep conserves much energy in such mammals, in particular because it can also develop into a torpor, whereby the metabolic rate drops significantly for a few hours during the sleep period. On the other hand, humans can usually rest and relax quite adequately during wakefulness, and there is only a modest further energy saving to be gained by sleeping. We do not enter torpor, and the fall in metabolic rate for a human adult sleeping rather than lying at rest and awake is only about 5–10%.

The beginning of health is sleep.

Irish proverb

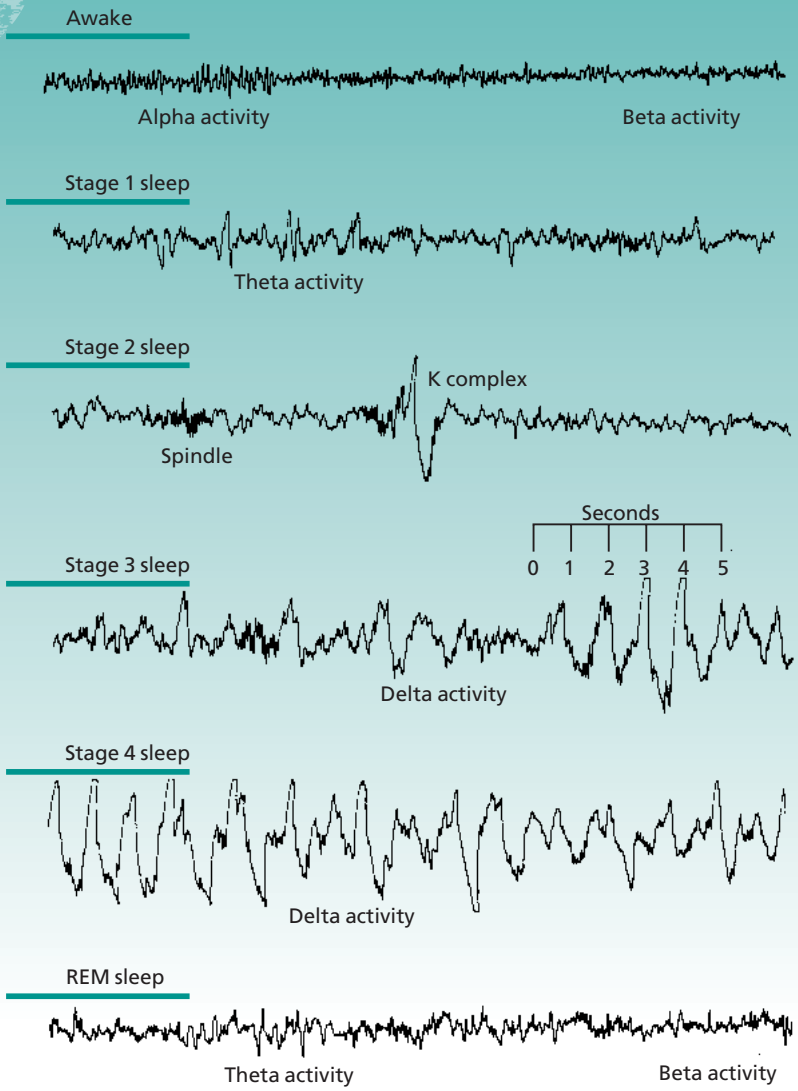

Fig. 1. EEG of human sleep stages. Wakefulness shows alpha activity (subject relaxed) and beta activity (alert). Theta activity can be seen in stage 1 sleep. Stage 2 sleep shows spindles and a K complex. Note the large slow waves (delta activity) of stage 4, also apparent to some extent in stage 3 sleep. Stages 3 and 4 together are 'slow-wave sleep.' The EEG of REM sleep resembles that of stage 1, and contains a mixture of beta and theta activities. To avoid mistaking these two stages, recordings are made of eye movements and chin muscle tonus.

It has been thought that sleep is a lesser form of hibernation, and although those small mammals which hibernate enter hibernation through sleep (via torpor), more recent and intriguing evidence indicates that the two states are distinct [2]. Hibernating mammals must periodically arouse and enter sleep, as it seems that a need for sleep also accumulates during hibernation. Such sleep periods involve a lengthy arousal from hibernation and are costly in energy terms. This strongly suggests that sleep must serve some vital function other than just energy conservation, even for these less cerebrally advanced mammals.

Sleep probably serves a variety of functions, which may well alter subtly as the evolutionary scale is ascended and depend on various interrelated characteristics of the mammal, particularly body size and the need to conserve energy, the level of cerebral development, the amount of time spent in relaxed wakefulness, type of diet, and whether it is a predator or prey. Also, for most mammals including ourselves, the roles of sleep may, for different reasons, alter during the night, initially serving more important purposes, then changing to those of less benefit, and eventually to a sleep that is superfluous, luxurious and just pleasant to take.

Perhaps sleep can be compared with eating and drinking? A certain amount is vital, but we can easily consume more than we really need. Just because we can, on days off, sleep an hour or so longer than usual does not mean that we really need this extra sleep. Currently this is a very controversial topic [3], and the counterargument is that because most people are able to take an hour or so more sleep than their usual daily 7–8 hours, then they must be chronically sleep deprived. This is the same as claiming that all drinking and eating is physiologically necessary, including the eating of luxury foods such as cakes, chocolate and ice cream. When people are encouraged to take as much sleep as they can, their daytime alertness is only improved marginally, mainly in the early afternoon [3]. If this regimen is continued for several days and nights, then nighttime sleep quality deteriorates, and people find that it takes longer to get to sleep at night and they wake up more frequently. It is as if their sleep is becoming stretched out, inefficiently, to fill the extended time available for it. Lying in bed in the morning to obtain more sleep is not cost-effective timewise, especially as in healthy people the simplest remedy for daytime sleepiness is a short nap. There is no substantive evidence to show that our daily amount of sleep has declined much over the course of history, and evidence to the contrary is very debatable. Recently, for example, Bliwise [4] claimed that people are more sleepy nowadays than 60 years ago, implying that we now take less sleep than we did then. But his sample from the 1930s contained very few subjects aged over 55 years, whereas almost 30% of the present-day sample were over this age limit. It is well-known that daytime sleepiness is greater in older people, and his conclusions could be the result of subject bias.

Measuring Human Sleep

The human sleep EEG is obtained from innocuous electrodes glued to the scalp and able to detect the relatively low electrical activity generated largely by the cortex. For animals, these electrodes are usually placed on or within the brain, and the EEG can be a little different from that obtained by scalp electrodes.

Much of human sleep can be assessed from the EEG alone (fig. 1). But for the determination of rapid eye movement (REM = 'dreaming') sleep, there is a problem. In primates, the EEG of REM sleep resembles that of stage 1 sleep, the lightest form of sleep (see below), and for this reason REM sleep used to be called 'stage 1 REM' sleep. The situation is different for most other mammals, where the EEG of REM sleep resembles that of an alert waking state, and for this reason is often also called 'paradoxical sleep' (i.e. the animal is asleep but the EEG indicates wakefulness). So, for one reason or another, additional measures have to be used to detect REM sleep. Electrodes are placed around the eyes to detect the rapid eye movements and over muscles in the chin or neck to measure the tonus of resting muscle. For reasons that are not understood, these particular muscles relax profoundly in REM sleep, as their resting tonus is lost. Although other voluntary muscles throughout the rest of the body do not lose this tonus, they are unable to move, so there is a generalized 'atonia' (i.e. paralysis of voluntary movement) during REM sleep. The locus ceruleus (situated in the brainstem) is responsible for the paralysis, and its destruction (in cats) produces 'REM sleep without atonia,' whereby the sleeping cat moves about in bursts of activity, seemingly enacting its dreams.

Rapid eye movements themselves occur in phases or bursts, occupying about one third of REM sleep. This 'phasic' activity is particularly intriguing and can be seen within the brain as bursts of 'pontogeniculo-occipital' waves, and externally in the limbs as twitches or, during REM sleep without atonia, as more intense movement, with the cat often seeming to be searching around quickly in what appears to be rapid reorienting to a succession of new and imagined stimuli.

The amount of sleep required by the average person is just five minutes more.

Anonymous

The EEG consists of waves that can be measured in terms of amplitude, which rises as sleep becomes deeper, and in terms of frequency [number of waves per second and expressed as 'hertz' (Hz), cycles per second], which falls with deepening sleep. In sleep, the effective frequency range for the human EEG is from about 0.5 to around 25 Hz, although there is other interesting EEG activity up to and around 40 Hz. Generally speaking, EEG frequencies below 3.5 Hz are referred to as 'delta' or 'slow-wave activity' (SWA), which has a high amplitude and is prolific in the deeper sleep stages 3 and, especially, 4 [5]. Other EEG frequency bands can readily be identified in sleep, especially 'theta' activity, which is typical of drowsiness and the lightest sleep (stage 1). In contrast, 'beta' activity, typically 15–25 Hz, consists of fast waves of low amplitude that are found mostly in the waking, alert cerebrum. 'Alpha' EEG activity is in the range 8–11 Hz and appears during relaxed wakefulness, when there is little or no visual input (especially when the eyes are shut or staring at a blank wall). There are some other, more transient, EEG activities found only during sleep, such as 'K complexes' and 'spindles,' which are both most evident in stage 2 sleep. The former seems to be associated with brief arousals, often in response to external stimuli, and the latter more with the brain's active blocking of arousals.

The division of non-REM sleep into stages 1–4 is rather arbitrary [5], but is, nevertheless, still generally accepted. Stage 1 is really a transition from wakefulness or drowsiness to what many view to be 'real sleep' (stages 2–4 and REM sleep), and in healthy, adult, good sleepers usually occupies only about 5% of the night. In this stage there is also much slow 'rolling' of the eyes up and down, with the eyelids slowly closing and opening. This can easily be seen when watching someone fall asleep. Much of human sleep, around 45%, is made up of stage 2 sleep. Stage 3 is more of a transition phase from stage 2 to stage 4 sleep, comprising about 7% of sleep, and containing up to 50% of SWA. When SWA exceeds this level, then the 'deepest' sleep, stage 4, is reached, comprising about 15% of sleep in the young adult. As can be seen from the 'hypnogram' in figure 2, sleep stages cycle throughout the night, REM sleep appearing about every 90 min in human sleep, with each episode lasting around 20 min, and in total constituting 20–25% of sleep. Two other characteristics of sleep seen in this hypnogram are a rapid descent to stage 4 sleep soon after sleep onset, and a prevalence of stages 3 and 4 sleep in the first two sleep cycles. The first period of REM sleep is usually a little shorter than the average.

Why Do We Sleep?

Theories about the functions of sleep date back thousands of years. Most people see the purpose of sleep in terms of rest and recovery from the 'wear and tear' of wakefulness. One cannot really argue with this idea as it makes so much sense, and besides, we all know that we feel 'the worse for wear' without sleep, and so much better after sleep. However, there is little or no evidence that outside the brain any other organ undergoes a heightened degree of repair during sleep [1]. All the evidence so far shows that these other organs undergo their restoration equally effectively (and probably more so) during relaxed wakefulness. The stimulus to the repair of tissue wear and tear is an increase in amino acid levels in the blood following food absorption by the gut. These amino acids are selectively taken up by cells to be synthesized into new protein (i.e. anabolism) to replace old and degraded protein (tissue is largely composed of protein, apart from water). This repair is facilitated by physical rest, but it does not have to be sleep – relaxed wakefulness is sufficient. During human nighttime sleep, blood amino acid levels usually fall, because we are not eating and, consequently, tissue repair is reduced. Anabolism requires a lot of energy, and it has been estimated that well over a half of our resting metabolic rate is due to anabolic activities. If these increased significantly throughout the body during sleep, then the metabolic rate and oxygen consumption would rise substantially. This does not happen; indeed they fall somewhat.

Humans show a marked surge in growth hormone output during the early part of sleep, which is largely associated with sleep stages 3 and 4. If one remains awake at this time, this surge is absent. This sleep-related growth hormone release is rare in other mammals and has little to do with tissue growth and repair, at least in the adult human. It is probably linked to the rather unusual fasting state which develops in human sleep, and it should be remembered that human nighttime sleep tends to be quite lengthy in comparison with that of many other mammals, few of which actually enter a fasting state during sleep. Herbivores continue to digest food throughout their sleep, carnivores gorge themselves on meat which can take up to a day to digest, and rodents wake up periodically to nibble more food. The human sleep-related growth hormone surge may be a mechanism to protect tissue protein against potentially detrimental effects of this fast, and also to promote the body's mobilization of its fat reserves [1].

Cell division in many tissues also shows a daily surge late at night and in the small hours of the morning, often coinciding with sleep stages 3 and 4 and the growth hormone rise, again suggesting that sleep promotes general growth and repair. However, the increase in mitosis is not due to sleep, or to growth hormone, as it is still evident if one remains awake at this time. This daily cycle in cell division is largely associated with feeding activity and a sleep-independent circadian rhythm. An increase in mitosis typically occurs a few hours after a meal (i.e. allowing for preliminary digestion, food absorption, cell repair and growth), particularly when we are resting.

REM Sleep

Many of the theories about the function of sleep concentrate on REM sleep, and many people believe that we only go to sleep for the purpose of dreaming or having REM sleep. We possibly dream in the same style as we think during wakefulness, and as most dreams are made up of an amalgam of the previous day's thoughts and events, dream 'interpretation' can only be accomplished by knowing about these idiosyncratic phenomena.

Dreams total around 100 min a night, but we can seldom recollect more than a few minutes worth. Dreams cannot be remembered unless one wakes up out of one and immediately thinks about it, when it can then be stored in one's memory. Dreams are probably meant to be forgotten, but I'll put that debate to one side and focus instead on the biological, rather than psychological, roles of REM sleep.

REM sleep may well stimulate and tone up the sleeping brain, preparing it for wakefulness. People can be deprived of REM sleep for months at a time through the use of drugs such as the tricyclic antidepressants which are typically used to treat depression. Most (not all) of these tricyclics suppress REM sleep very effectively. If REM sleep played some vital role with regard to memory, as is often believed, then this loss of REM sleep for such a long period would be expected to have a major impact on memory. But depressed patients treated with tricyclics show no memory impairment.

Whatever roles REM sleep may have, these may center on the developing brain – in the majority of mammals, REM sleep is most prolific in the developing fetus. One of the most plausible theories for this is that REM sleep helps brain development by providing some sort of substitute stimulation for the brain, owing to the relative lack of external stimulation from within the uterus.

Whilst REM sleep has traditionally been seen to offer benefit to the brain, non-REM sleep, particularly SWA, has been viewed as facilitating repair for the rest of the body. 'Dualism,' the body versus mind controversy in biology, has strongly, but erroneously, influenced perspectives on sleep. However, apart from anything else, one must not fall into the

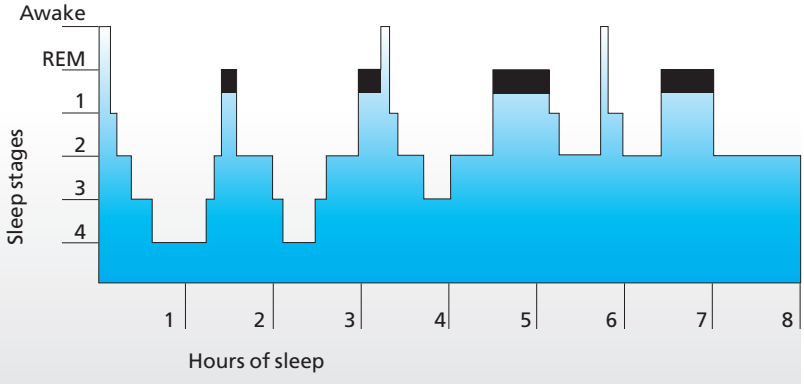

Fig. 2. A simplified 'hypnogram' of sleep stage changes over the night in young human adults.

trap of thinking about each type of sleep in isolation, each having its own distinct function separate from whatever the other types of sleep are doing. Sleep is a complex process and it is likely that different types of sleep interact with one another to promote a variety of functions.

Other Sleep Theories

Apart from viewing sleep as some sort of recovery process, most of the early theories about sleep function only looked at the 'how' of sleep and mechanisms that produce sleep, rather than at what sleep does, for example believing sleep to be the result of a buildup of some substance in the brain during wakefulness that is dissipated during sleep. Even Aristotle thought along these lines 2,000 years ago, and considered that sleep resulted from warm vapors rising from within the stomach.

In the last century, with advances in understanding of the brain, heart and vascular system, one school of thought considered sleep to be caused by the 'congestion of the brain' by blood. This contrasted with another popular theory at the time of 'cerebral anemia,' due to blood being drawn away from the brain and diverted elsewhere in the body, especially to the gut. Such ideas even led to opposing beliefs about how to induce 'better' sleep. Some authors propounded sleeping without pillows to encourage blood flow to the head, while others encouraged the opposite – the use of plenty of pillows to drain the blood away. 'Behavioral' theories were also common in the 19th century, particularly that sleep was due to an absence of external stimulation, with wakefulness only being possible if the organism was constantly stimulated: take the stimulation away and the animal will fall asleep. To some extent this notion is true, as we can all testify, but it is not the answer.

At the turn of this century, a popular view was that sleep was not so much a passive response but an active process like an instinct, to avoid fatigue. At this time there were also many 'humoral' theories proposing that various sleep-inducing substances accumulated in the brain. These ranged from known chemicals like lactic acid, carbon dioxide and cholesterol, to the vaguely described 'leucomaines' and 'urotoxins.' Nevertheless, in 1907, some headway began to be made when two French researchers, René Legendre and Henri Pieron, claimed to have obtained a substance they called 'hypnotoxin' from sleep-deprived animals. This gave a large boost to the humoral theories for the next 20 years or so, with much activity by several groups of researchers. However, success was hard to come by and interest dwindled. That is, until the 1960s, since when great headway has been made into 'sleep substances.'

In those interim years there were advances in neurophysiology relevant to sleep, and a spate of different neural 'inhibition' theories for sleep appeared. Many had had their early impetus from Pavlov's views on 'cortical inhibition' – that sleep originated from a form of blocking within the cerebral hemispheres. Although Pavlov dismissed the alternative, of sleep-inducing 'centers' in more basic parts of the brain below the cortex, these have since been found to exist and have become the focus of one of the prominent fields of sleep research, especially since the discovery in the late 1940s of arousal centers in the reticular formation. Nevertheless, sleep centers and humoral theories still do not tell us much about the purpose of sleep, in the same way that knowing about centers in the brain that regulate eating behavior explain little about the purpose of eating.

Sleep Deprivation

One obvious route to understanding what sleep does is through total deprivation of sleep. In humans, with the exception of the brain, sleep deprivation is surprisingly uneventful for the rest of the body. But there are still gaps in our knowledge, especially in relation to the immune system. There is no strong evidence to show that the human immune system is rejuvenated during sleep. In humans, sleep deprivation causes changes to certain aspects of host defense, but these are not impairments, and are best described as adjustments due to an increased surveillance by the immune system, which return to 'normal' after recovery sleep.

Over the last 15 years, substantial sleep deprivation work has been undertaken with rats. Animals deprived of all sleep die after about 14 days, for reasons that are still not clear. In the course of this deprivation they show reliable and consistent changes. There is an initial body temperature rise, which then for a while returns to normal. The animals eat voraciously, but lose weight and develop malnutrition-like symptoms. The output of thyroid hormones falls, whereas catecholamines (adrenaline and noradrenaline) rise – changes obviously linked to those of eating and body weight. The rats develop peculiar necrotic skin lesions, and in the final stage of sleep deprivation, body temperature drops and weight loss continues. The weight loss at death is far less than that seen when rats die of starvation alone.

Exactly why these animals die still remains an open question, as there is no obvious cause. Rats allowed recovery sleep towards the end of this terminal phase generally recover fully, and very quickly (although some still die). No organ apart from the skin seems to show signs of failure. Whether or not the immune system fails is a matter for much debate. Two views have been generated despite their advocates using very similar experimental procedures with rats. Everson [6] in Memphis argues that sleep-deprived animals develop widespread systemic infections due to a breakdown of the immune (host) defense system, with bacterial toxins building up in the blood, while Bergman et al. [7] in Chicago found that sleep-deprived rats have little by way of serious infections, and treating animals with antibiotics to remove any signs of infection neither affects the temperature and weight changes, nor prolongs progression towards death. It should be noted that infections in rats do not generally cause fever – often the opposite.

Many studies have deprived humans of sleep, usually for around 1–3 days, and a few for 5–8 days [1]. There are no reports of physical illness, and no hormonal signs of any alarm response – there is simply a general physiological slowing up. In humans, minor changes or resettings occur in the regulation of certain physiological processes, particularly thermoregulation. However, this is very minor, for example body temperature drops by about 0.5 °C and then stays there. This nil outcome with respect to body functioning, from over 50 sleep deprivation experiments on humans, is not what might be expected from a viewpoint that sleep is a condition of heightened tissue growth and repair, overcoming the wear and tear of wakefulness. It seems that for us, these restorative processes are carried out effectively during the wakefulness of sleep deprivation.

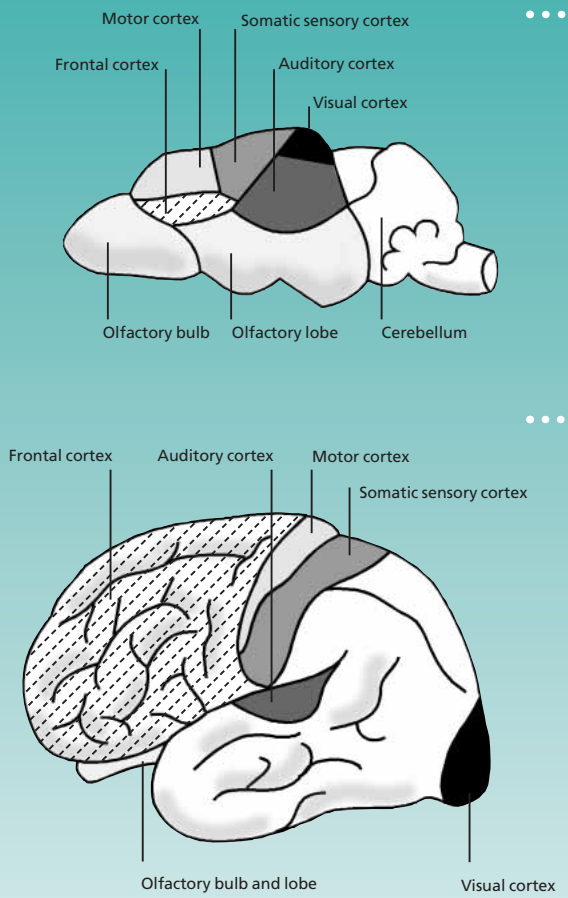

Fig. 3. Schematic side views of the brains of a shrew and a human (not drawn to scale). Apart from having a very much smaller brain in proportion to its body size, the shrew has a poorly developed cortex, but well-developed olfactory bulb and lobe. Humans have a relatively huge cortex, a massive frontal cortex, but only a rudimentary olfactory region. The frontal area is almost nonexistent in the shrew. If sleep offers a special form of recovery for the cerebral cortex, particularly for the frontal area, then in these respects it is likely that sleep function will differ radically between these two mammals.

Sleep and the Human Cerebral Cortex

Unlike many organs, the cerebral cortex is unable to switch off to any degree outside sleep. Even when we lie down, turn off the light, relax but remain awake, block out sound and try to clear our minds of all thoughts, the cortex is always in a state of quiet readiness, prepared to respond immediately to any stimulus. In this respect, the waking cerebrum is like a computer, where the power consumption is near to its peak whether it is idling on standby, awaiting instructions or involved with programs and taking in information.This may be why the obvious effects of human sleep deprivation are on behavior, because the cerebrum needs to sleep, and cannot obtain any rest during wakefulness. If such rest is required for the recovery and restitution of neural and related tissues, then sleep is the only provider of this facility. The more advanced the cerebrum, as in humans, the greater the role sleep may have in this recovery (fig. 3).

Sleep that knits up the ravell'd sleave of care,
The death of each day's life, sore labour's bath,
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast.

William Shakespeare, Macbeth

Most standard psychological tests are generally unhelpful from the viewpoint of sleep function. They are far too simple, unstimulating and tediously boring. This is why they are very sensitive to sleep loss, but if sleep-deprived subjects are motivated to do well at the task then the performance deficit can be reversed. Hence, these tests simply measure tolerance to boredom, which shortens with sleep deprivation, and tell us little about the sleep function with respect to the cerebral cortex. So let me take another perspective. The most metabolically and neuronally active part of the waking cortex is the frontal cortex, which comprises over 30% of the cerebrum. It is responsible for directing and sustaining attention, inhibiting distraction by other stimuli, planning many aspects of behavior (including speech), running the working memory and innovative and flexible thinking. If sleep provides cerebral recovery, then this busiest part of the cortex may require the most recovery during sleep and, if so, it may be the first to start faltering during sleep loss. The types of (neuro)psychological tasks needed to test this hypothesis have to be much more subtle than the more usual tests used to measure sleep loss. This is the approach that our own research has taken [8], where we have found that despite the subjects' best efforts to perform well, one night of sleep loss impairs the ability to comprehend a rapidly changing situation, increases distraction by irrelevant information, makes people think and plan in a more rigid and less flexible way, perseverate more and be less able to produce innovative solutions to problems. The number of words in one's vocabulary is reduced both verbally and in writing, articulation becomes more labored and intonation flatter. All these effects certainly suggest a deterioration within the frontal cortex, and are pertinent to many real-world situations and for those people working without sleep.

As for the type of sleep that might particularly facilitate cerebral recovery, SWA more than any other type of sleep seems the best suited. It is the form of sleep most highly correlated with the length of prior wakefulness. When we go to sleep there seems to be great pressure to obtain SWA, which takes precedence over all other sleep states. SWA best fits a restorative role. More importantly, SWA is particularly evident in the frontal cortex, and brain scanning measures of cerebral metabolism show what appears to be the greatest degree of cerebral shutdown occurring during SWA, especially in the frontal region.

Inasmuch as human sleep seems to provide a vital role for the frontal cortex, and since this brain region is only poorly developed in the rodent and other less cortically advanced mammals, the functions of sleep have probably changed somewhat during mammalian evolution. Perhaps beginning largely as an immobilizer and energy conserver, it has evolved for us as a facilitator for the recovery of high-level cerebral function.

Professor Jim Horne runs the Sleep Research Laboratory at Loughborough University, UK, and is the editor of the Journal of Sleep Research, one of the two international journals devoted to sleep research. His main interests are the functions of human sleep and the consequences of sleep loss and sleepiness.

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Sleep and Immune Function

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Common knowledge of sleep is replete with "old wives' tales." Two perhaps are told to almost everyone by a loving parent or grandparent: if you don't sleep enough you'll get sick and, conversely, if you're ill, sleep will help you recover. Despite the fact that even Hippocrates dispensed similar advice and they seem such common and sensible suggestions, these postulates received scant scientific attention until recently. It is only in the last 10 years that we have begun to address the questions of whether sleep loss affects host defenses and whether sleep is altered during infection and helps in recuperative processes. This article reviews some of the recent findings in this field, which do indeed suggest that induced sleep loss affects host defenses and that sleep is likely to be beneficial for recovery from infectious diseases.

Sleep Deprivation and Host Defense

Among the possible functions proposed for sleep, an immune system function did not receive much attention until recently. This may have been due, in part, to a scientific emphasis on parsimony – seeking the simplest explanation for a biological event. Since sleep is such a time-consuming state, it was thought that sleep deprivation should produce a specific, obvious, and dramatic deficiency, much like the removal of an organ. Our thinking has now changed and we no longer expect to find one big functional deficiency induced by sleep deprivation. Rather, sleep deprivation appears to induce a series of homeostatic responses aimed at protecting the integrity of the organism. Physiological changes resulting from sleep deprivation develop slowly, and it takes many days for clinical signs to become apparent. This is similar to what happens during food or water deprivation. These deprivations of basic bodily requirements do not produce malfunction in the short term but over the long term, they are lethal.

Anecdotal evidence suggests that during short-term sleep deprivation we are more vulnerable to infections of the upper respiratory tract. But experimental studies in humans have been unable to show an increased occurrence of illness related to sleep loss. However, the drawback of such studies is that subjects are typically well rested beforehand and kept fairly isolated and comfortable during the study to avoid potentially confounding variables. The experimental environment, in other words, offers them some protection from exposure to pathogens. The ramifications of sleep deprivation are expected to be much greater for someone whose health is compromised than for a normal experimental subject sleep deprived on an acute basis. Sleep disruption is indeed a risk factor for increased mortality, and it is believed to exacerbate disease processes.

In contrast to human work, animal studies can address sleep-loss-induced changes in host defenses more directly. Brown and his colleagues in Australia have studied the responses of sleep-deprived mice to a primary infectious challenge [reviewed in ref. 1]. Influenza virus was inoculated twice, 7 days apart, into the gastrointestinal tract. A week later, the animals were given live virus intranasally. Half of the mice were then sleep deprived for 7 hours, and half were allowed to sleep normally (a mouse typically sleeps 11 or more hours each day). Three days after the challenge, mice that had slept normally had completely cleared the virus from their lungs, but virus clearance was incomplete in mice deprived of sleep. These findings suggest immune suppression of the respiratory tract due to sleep deprivation. Since influenza virus kills many more people each year than e.g. HIV, these potentially important findings should be verified, and the experiment extended to humans.

The same group also investigated antibody production in sleep-deprived rats and found that it was suppressed [reviewed in ref. 1]. Rats were injected twice subcutaneously, 2 weeks apart, with a commonly used antigen, sheep red blood cells. After the second administration, the rats were given one of three agents: (1) saline as control, (2) the cytokine interleukin (IL)-1, or (3) the bacterial cell wall component, muramyl dipeptide. They were then either sleep deprived for 8 hours or allowed to sleep normally. Sleep deprivation reduced antibody levels in the serum, but this suppressant effect was eliminated if the sleep deprivation was combined with administration of IL-1 or muramyl dipeptide, factors that might have stimulated the immune system, overriding the suppressant effects of sleep deprivation.

However, short-term sleep deprivation has also been shown to be associated with an enhancement of host defenses. Bergman and colleagues at the University of Chicago have demonstrated the suppression of experimentally induced tumor growth in sleep-deprived rats. In this case, sleep deprivation appears to have an adaptive advantage in combatting subdermal foreign agents [reviewed in ref. 1].

Short-term sleep deprivation in humans, uncomplicated by physical regimens or other experimental stressors, seems to evoke

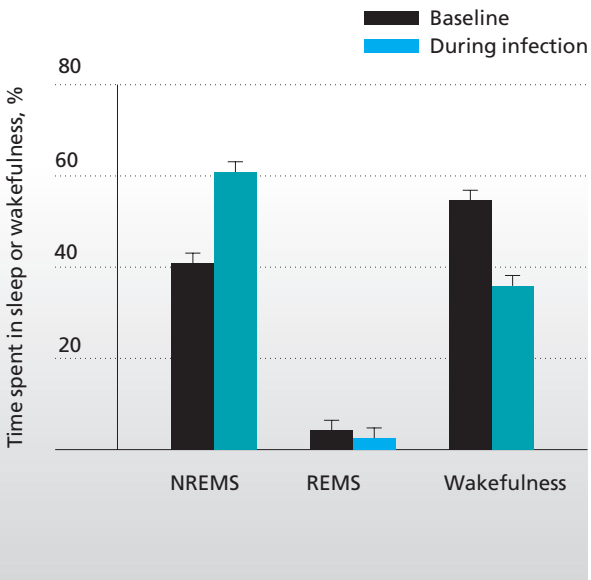


Fig. 1. Influenza virus infections in mice are associated with a prolonged increase in NREMS and decrease in REMS and wakefulness. Shown are averages from 3 days of baseline recording and 3 days after intranasal inoculation of mice with H1N1 influenza virus. Data provided by J. Fang.

Sleep is that golden chaine that ties health and our bodies together.

Thomas Dekker

the first line of host defense [reviewed in ref. 1]. One common sign is a rise in the number of circulating white blood cells. Over 2 nights and 3 days of sleep deprivation, this rise is followed by an increase in natural killer cell number and cytotoxicity. Despite conventional wisdom, activation of the hypothalamic-pituitary-adrenal (HPA) axis, indicative of emotional distress and immunosuppression, is not found in sleep deprivation studies that control for extraneous variables. At least five independent laboratories have demonstrated that the ability of circulating immunocytes to produce immune response modifiers, such as IL-1, tumor necrosis factor (TNF), interferon-γ, or IL-6, is enhanced by sleep deprivation [2]. These changes hint at an increased communication among and/or activation of other cells. Nevertheless, the functional implications of an increase in circulating host surveillance mechanisms are unclear, and determining their maladaptive versus regulatory nature awaits further study.

The Septicemic Sleep Deprivation Syndrome

Long-term sleep deprivation in rats produces a reliable syndrome-like series of physical changes. To deprive a rat of sleep, when the electroencephalogram and other instruments indicate sleep onset, the animal is kept awake by forced walking. To control for stress effects, a control animal is paired in the experimental setup with the sleep-deprived rat. It can sleep when the sleep-deprived animal is awake, but not when the sleep-deprived rat is trying to sleep. The sleep-deprived rats show progressive development of a marked negative energy balance (manifested by dramatic increases in food consumption and loss of body weight), a decline in plasma thyroid hormone concentrations to very low levels (due to a change in central regulation), and sympathetic activation without HPA axis overactivation [reviewed in ref. 3]. These changes culminate in lethal sepsis, manifested by bloodstream infection preceding a cachectic-like moribund state comprising the last hours or days of survival. The septicemia is not accompanied by fever or marked tissue inflammation, indicating that profound alterations to the host defense mechanisms must have occurred [4].

At the onset of septicemia, sleep-deprived rats remain motorically active and many are hyperphagic. Therefore, the breakdown in host defense processes is antecedent to severe morbidity. The signs that follow are consistent with the expected outcome of the cytokine- and endotoxin-mediated pathology characteristic of lethal sepsis and shock. The bacteria that have been cultured from the bloodstream of sleep-deprived rats are mostly facultative anaerobes, indigenous to the host and the environment, the same virulent microbes that threaten patients with suppressed immune systems, e.g. *Pseudomonas aeruginosa, Streptococcus agalactiae*, and *Klebsiella pneumoniae*. Detection of virulent opportunistic microbes in the blood of sleep-deprived rats is evidence of a functional impairment. Once host defense systems have been breached, the deleterious effects could be triggered by a number of nonbacterial agents known to cause similar metabolic derangements, e.g. endogenous cytokines, viruses and fungi.

The breakdown in host defense and the likelihood of immune compromise in sleep-deprived rats is the first physiological consequence of sleep deprivation to be identified that has obvious clinical significance. Studies are underway by my colleagues Everson and Toth to determine the timing and location of host defense breakdown in sleep-deprived rats. Preliminary evidence suggests that bacteria translocating from the gut are one source of infecting pathogens. Bacterial translocation can occur as a consequence of decreased local immunity, and it is expected to lead to increased pathogen adherence, proliferation, and penetration. Everson is also determining whether decreased resistance to infectious disease in sleep-deprived rats arises from a direct effect of sleep deprivation on immune function or indirectly through hormonal and metabolic changes, such as low plasma thyroid hormones.

How Sleep Responds to Infection

Most of us are subjectively aware of the many central nervous system manifestations of infection, e.g. loss of appetite, fever, inactivity, social withdrawal and somnolence [reviewed in ref. 2]. Indeed, fever and somnolence have been hallmarks of illness throughout medical history. Fever has been extensively studied, but sleep responses during infections were ignored for over two millennia from the time that Hippocrates acknowledged disease-associated sleep responses until the mid-1980s.

The first efforts to quantify sleep changes over the course of a microbial infection were published by Toth and Krueger [5]. Rabbits were inoculated intravenously with gram-positive bacteria (*Staphylococcus aureus*) and sleep was recorded for the next 2 days. For the first 18–24 hours, non-rapid eye movement sleep (NREMS) greatly increased and was accompanied by an increase in electroencephalographic slow-wave activity, thought to be indicative of a greater intensity of NREMS. Thereafter, both measures decreased for about another 20–24 hours. Throughout this 48-hour period, rapid eye movement sleep (REMS) was inhibited and the animals had fevers and the other usual signs of infection, e.g. neutrophilia. In several subsequent experiments, rabbits were infected with other gram-positive bacteria, gram-negative bacteria, fungi (e.g. *Candida albicans*) and protozoans (e.g. *Trypanosoma brucei*). Every time, there was an induction of the biphasic NREMS response and inhibition of REMS, although the timing depended on the route by which the microbe was administered, the light/dark cycle, and the species of microbe used. NREMS responses to intravenously inoculated gram-negative bacteria, for example, tended to be very rapid in onset: the increase lasted only 6–8 hours, whereas the period of reduced NREMS was prolonged.

Two findings from this series of experiments emphasize just how much remains to be investigated. In one experiment, rabbits were put in either a constant-light or a constant-dark environment and then inoculated. Compared to animals in a 12 hour:12 hour light:dark cycle, the characteristic initial NREMS increase in animals in constant light was greatly augmented, while the animals kept in constant dark showed great enhancement of the later NREMS inhibitory response. As yet, we do not know the reasons for these diametrically opposite responses.

In another study, the disease commonly called sleeping sickness was studied in rabbits. Animals infected with *T. brucei brucei* exhibit parasitemia approximately every 7 days during the initial weeks of the disease. These periods of parasitemia are associated with increases in NREMS superimposed, however, on a longer-term trend of decreasing NREMS over the course of several weeks. Nevertheless, since each episode of parasitemia presents an immune stimulus to the host, the results are consistent with the hypothesis that immune stimulation is correlated with somnolence.

Viral diseases are also associated with changes in sleep. Humans infected with HIV, but not having AIDS, show an excess of deep NREMS in the latter half of the night. In contrast, after AIDS develops, sleep is greatly disrupted. Rabies viral infections are also associated with sleep changes in animals. However, both HIV and rabies viruses are trophic to the brain and it is difficult to distinguish virus-induced tissue damage effects from virus-induced immune effects on sleep. But influenza infections in mice and humans are initially localized to the lung. Sleep in influenza-infected mice is greatly altered over many days (fig. 1). The profound increases in NREMS responses are similar to those observed after bacterial challenge but last throughout the 3-day postinoculation period. REMS was inhibited during the 3-day postinoculation period as was wakefulness.

Whether sleep responses to infectious challenge are beneficial to host defenses remains an unanswered question. However, there is a correlation between an animal's ability to survive an infection and the amount of time spent in NREMS during the first 12 postinoculation hours (fig. 2).

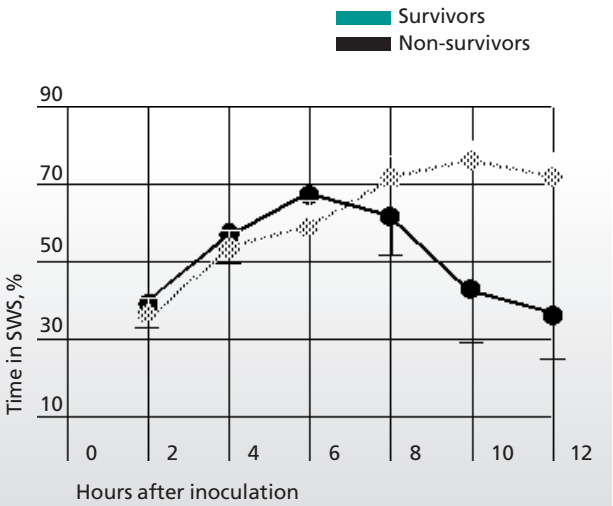


Fig. 2. Changes in slow-wave sleep (SWS) predict whether an animal will survive an infection. Animals that slept more during the first 12 hours after infectious challenge were more likely to survive the disease than animals that failed to enhance their duration of SWS. Data provided by L. Toth.

N-Acetyl-muramyl-
L-alanyl-*D*-isoglutamine

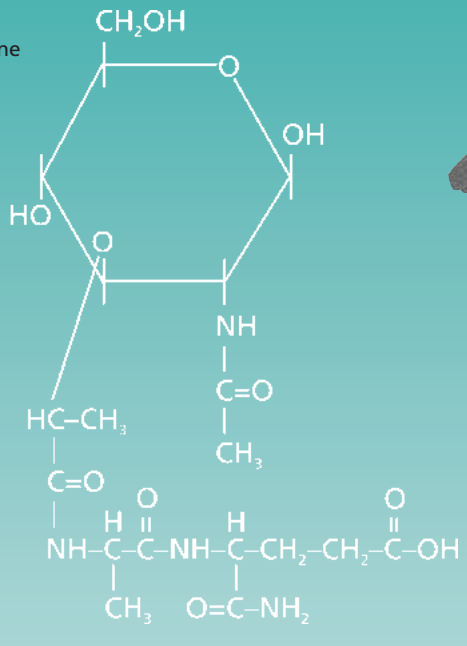


Fig. 3. The structure of muramyl dipeptide (MDP). MDP is derived from bacterial cell wall peptidoglycan. While digesting bacteria, macrophages release similar muramyl peptides which are somnogenic. Somnogenic muramyl peptides can also be extracted from mammalian tissues such as brain and urine. Muramyl peptides also play a role in other host defense mechanisms such as fever and antibody production.

I did not sleep.
I never do
when I am overhappy,
over-unhappy,
or in bed
with a strange man.

Edna O'Brien, The Love Nest

Research in this area began as an outgrowth of the search for endogenous sleep-promoting substances. One somnogenic substance identified in the early 1980s is a muramyl peptide (fig. 3). Muramyl peptides are well known as the monomeric building blocks of bacterial cell wall peptidoglycan. At the time of their isolation from mammalian tissues, it was assumed that they were derived from bacteria since there are no known synthetic pathways in mammals for some of the components in muramyl peptides. As I have already mentioned, preliminary evidence has shown that sleep loss affects bacterial populations within the gut, which likely results in translocation of bacteria across the intestinal wall. Furthermore, mammalian macrophages enzymatically tailor somnogenic muramyl peptides from bacterial cell walls and release them into the surrounding extracellular fluid. And, finally, somnogenic muramyl peptides stimulate cytokine production. Collectively, these findings lead to the hypothesis that gut bacteria are affected by and affect sleep, adding yet another exciting dimension to endosymbiotic relationships.

Mechanisms of Microbial-Induced Sleep Responses

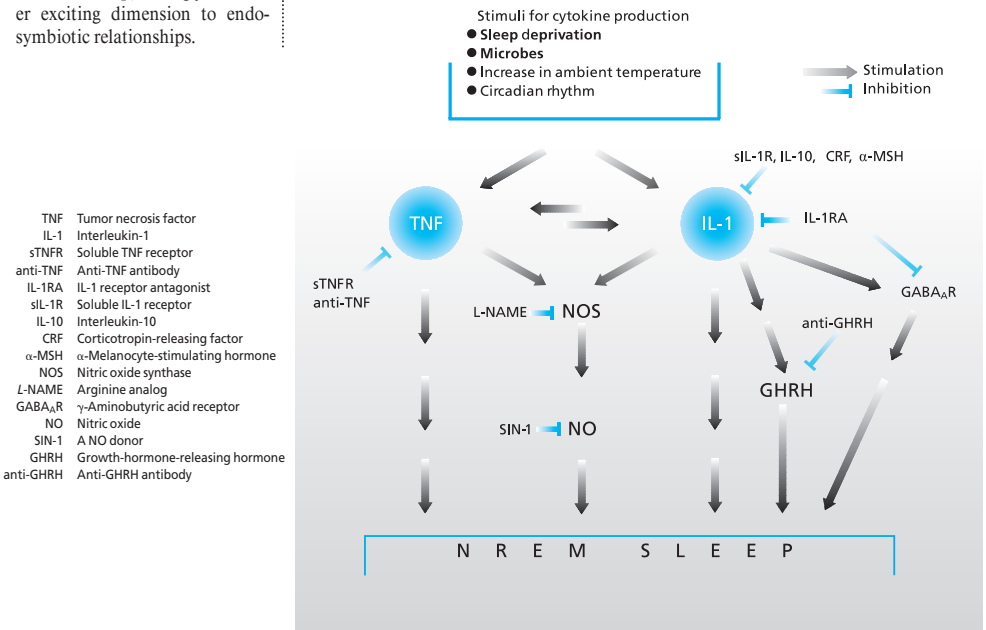
Infection is associated with the up-regulation of a wide variety of immune response modifiers and endocrines. One class of immune response modifiers tied to sleep regulation are the cytokines such as IL-1β and TNF-α. Exogenous administration of these cytokines to experimental animals induces excess NREMS while inhibiting REMS, reminiscent of sleep responses occurring during infection (see fig. 1). However, high doses of IL-1 inhibit, rather than promote, NREMS, and in fact very high doses induce symptoms characteristic of septicemic shock. This latter observation tempts one to speculate that the nonsurvivors in figure 2, which have had less sleep, are producing excess IL-1.

There are other data to suggest that IL-1 and TNF are involved in physiological sleep regulation. (1) Inhibiting IL-1 or TNF with antibodies or antagonists directed against them inhibits spontaneous sleep in normal animals – it seems that basal levels of IL-1 and TNF production are responsible, in part, for sleep. (2) Sleep responses induced by sleep deprivation or by mild increases in ambient temperature are blocked if animals are pretreated with inhibitors of either IL-1 or TNF. (3) Knockout mice lacking either an IL-1 type I receptor or the 55-kD TNF receptor sleep less than other strains of mice. (4) The brain shows diurnal rhythms of IL-1β mRNA and TNF-α mRNA, the highest levels being found during periods of maximum sleep. (5) Levels of both IL-1 and TNF protein also vary with sleep-wake cycles in normal animals, and in humans, levels of circulating IL-1 and TNF change in phase with sleep-wake cycles. Together, such data strongly implicate IL-1 and TNF in physiological sleep regulation. And, since production of both these cytokines is increased by infectious challenge or after injection of a variety of microbial products, it is very likely that sleep responses induced by infection result from increases in IL-1 and TNF.

Infection is also associated with increased growth hormone (GH) release. IL-1 induces GH release via brain-derived GH-releasing hormone (GHRH). Blocking GHRH blocks IL-1-induced NREMS responses. Infection and cytokines also affect several other endocrine systems such as the corticotropin-releasing hormone–adrenocorticotropin-releasing hormone–glucocorticoid axis, which is usually turned on by stress. Many of the individual hormones in this axis inhibit, rather than promote, sleep. It is possible that the up-regulation of this axis is responsible for the increased wakefulness which follows some microbial-induced sleep responses (fig. 4).

Cytokines and other somnogenic growth factors likely regulate sleep via multiple interactions with neuronal networks [6]. The production of some of these growth factors seems to be dependent, in part, on neuronal use, and growth factors in turn may affect neuronal networks in two interlocking ways. First, they are believed to change the cellular composition of the circuits and their responsiveness to neurotransmitters. Second, they are possibly involved in sculpturing synaptic populations which, in turn, would affect circuit dynamics. This synaptic sculpturing process could be considered a function of sleep. Thus, sleep mechanisms (circuit dynamics) and sleep function (synaptic sculpturing) are inseparable since they affect each other and depend on the same growth factors.

These are exciting and challenging ideas for us to pursue. It is now becoming clear that sleep can affect host defense systems and that infectious challenge is associated with robust sleep responses. Step by step we are learning in detail why one of the oldest and most frequently prescribed medicines is – sleep.



TNF Tumor necrosis factor
IL-1 Interleukin-1
sTNFR Soluble TNF receptor
anti-TNF Anti-TNF antibody
IL-1RA IL-1 receptor antagonist
sIL-1R Soluble IL-1 receptor
IL-10 Interleukin-10
CRF Corticotropin-releasing factor
α-MSH α-Melanocyte-stimulating hormone
NOS Nitric oxide synthase
L-NAME Arginine analog
GABA$_A$R γ-Aminobutyric acid receptor
NO Nitric oxide
SIN-1 A NO donor
GHRH Growth-hormone-releasing hormone
anti-GHRH Anti-GHRH antibody

Fig. 4. Sleep and cytokines. Note the many possible interactions and the pathway redundancy which provides stability to the system. (Not all the substances that could be implicated in this network are shown.)

Acknowledgement

This work was supported in part by the National Institute of Neurological Disorders and Stroke (NS-25378, NS-31453, NS-27250).

James Krueger is Professor in the Department of Physiology and Biophysics at the University of Tennessee in Memphis. His current research is focused on the relationships between sleep and infectious diseases, the biochemical regulation of sleep, and brain organization and sleep function. He is a contributor to the forthcoming Karger publication, *Sleep Science: Integrating Basic Research and Clinical Practice,* and editorial board member of *Neuro-ImmunoModulation.*

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Desperately Seeking Sleep

A Portrait of the Sleep Clinic, Zurzach, Switzerland

Dr. Schwander (standing) and colleague at work in the sleep lab.

Sleep disturbances are among the most common health complaints in western populations. The Report of the National Commission on Sleep Disorders, released in the USA in 1993, revealed that as many as one-third of all American adults are affected by sleep disturbances, and about 40 million Americans suffer from chronic disorders of sleep and wakefulness. The majority of these disorders, though often severely disabling or even life threatening, remain undiagnosed and untreated, and cost society tens of billions of dollars annually due to decreased work performance, illness and accidents. Recent years have witnessed the establishment in many countries of sleep medicine clinics equipped to help those patients requiring more specialized care than the busy family practitioner is normally able to provide. The first such clinic in Switzerland opened its doors in autumn 1995 in Zurzach, a health resort located near the Rhine. The editors of the Gazette recently visited the clinic and interviewed its medical director, Dr. Jürg Schwander.

Dr. Schwander, why are we seeing the establishment of specialized sleep clinics in so many countries today?

Sleep disorders are increasing. The latest surveys verify this: every fourth person in Europe is affected by minor sleep disturbances, every twelfth by serious ones. Although only meagre epidemiological data are available in Switzerland, we know that sleep disorders are one of the most frequent health complaints after nervousness, headache, coughs and backache. As the causes of sleep disorders are so varied, sleep clinics and trained specialists are necessary to deal with the many facets of the problem. A multidisciplinary perspective is indispensable in this field of medicine. The cooperation of a range of specialists enables an exact diagnosis to be established as quickly as possible and the provision of optimal treatment for the patient. Although the field of sleep medicine got a late start – the first centers were set up in the USA in the 1970s and in Europe in the 1980s – it has since grown very rapidly.

What exactly is sleep medicine and what are the aims of the clinic in Zurzach?

Sleep medicine is a clinical subspecialty which deals with the diagnosis and treatment of patients who complain about disturbed sleep at night, excessive sleepiness during the day, or some other sleep-related problem. The existence of this field of medicine is based primarily on the fact that there are really two states of the actively functioning brain – awake and asleep. These states influence and complement each other. Sleep is often affected by problems during wakefulness and wakefulness is affected by disordered sleep. In addition, some physiological functions, breathing for example, are regulated differently awake and asleep and therefore may occur normally in the waking state but be pathological in sleep. Through its influence on physiological processes, sleep and the circadian phase at which we preferentially sleep modify a whole range of non-sleep disorders that are, or could be, modified by the sleeping state. The spectrum of problems dealt with in sleep medicine is very broad, ranging from difficulties in falling asleep to disorders such as sleep apnea, narcolepsy and addiction to sleeping pills. Our clinic's prime aim is to solve the sleep problems of patients, whatever they may be. We have the means to diagnose and treat all types of sleep disorders. Left untreated, sleep disorders cause personal suffering, decreased work performance, and risk of accidents in daily life and traffic. Breathing disorders during sleep increase the risk of high blood pressure, stroke and heart attack.

How is the clinic organized to achieve these aims effectively?

The patient is the focal point of all our activities. Most sleep disorders can be treated on an outpatient basis, but if further clarification is essential, we request that the referring doctor makes arrangements for the patient's admission to the clinic. The clinic has four modern sleep laboratories and eight beds for inpatients. Although meeting hospital standards, the rooms are pleasant and cosy because it is important that people feel at home here.

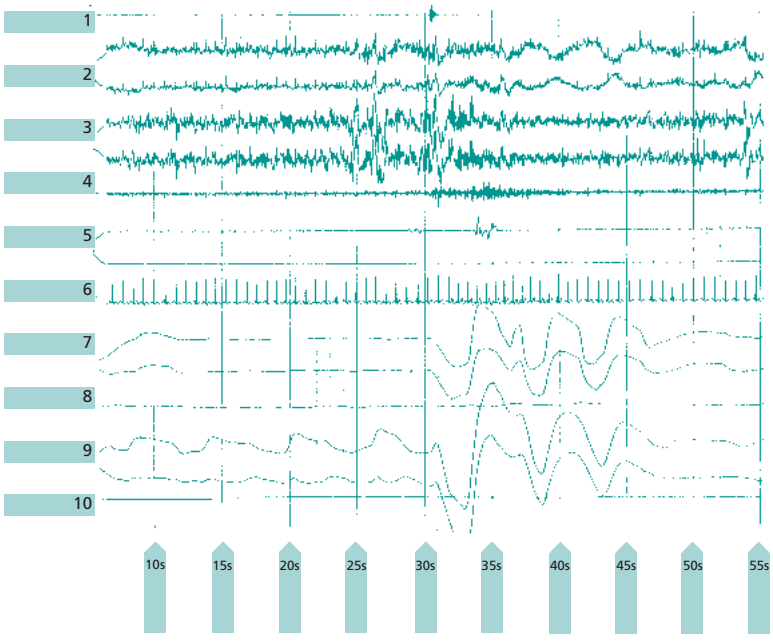

Fig. 1. Recording of a sleep apnea. The figure illustrates a 50-second excerpt from a nocturnal PSG recording of a patient suffering from obstructive sleep apnea syndrome. The displayed signals from top to bottom are: **1** sonogram (snoring microphone); **2** left and right electro-oculogram for eye movement recording; **3** electroencephalograms from the left and right hemisphere; **4** submental electromyogram; **5** actogram of movements of the left and right leg; **6** electrocardiogram; **7** airflow through the left and right nostril; **8** airflow through the mouth; **9** motions of the rib cage and abdomen; **10** oxyhemoglobin saturation. The left half of the tracing shows stage 2 sleep with an obstructive sleep apnea as indicated by cessation of airflow and by increasing motions (efforts) of the rib cage and abdomen. A resumption of breathing with a snort occurs in the middle, simultaneously with an arousal from sleep, evident from increased submental muscle activity, alpha and high-frequency activity in the electroencephalogram, and movement of one leg. Following the arousal, the patient falls back into stage 1 sleep, while the reduction of airflow towards the right of the recording heralds the next apnea.

As I mentioned previously, sleep disorders have such varied and complex causes that an interdisciplinary team of specialists is essential. Our clinic team currently consists of an internist (myself), a psychiatrist and a psychologist, and a sleep specialist supported by five qualified nurses with special training in sleep medicine. Depending on the individual case, we also consult with neurologists, cardiologists, pediatricians, as well as ORL and dental specialists. An advantage of our location in Zurzach is that we can, at any time, call on the expertise of the specialists in the adjoining rheumatism and rehabilitation clinic. Being a health resort, Zurzach has facilities such as thermal baths, and its location near the Rhine and Black Forest is conducive to rest and relaxation.

The clinic in Zurzach, Switzerland

What can patients expect when they come to you for the first time?

During the first visit to our outpatient clinic, a patient is interviewed by two specialists – separately so that he or she feels at ease. This enables us to make a first analysis of the problem and to decide on our next steps. The patient completes a sleep questionnaire and is asked to keep a diary of his or her sleep habits for 2 weeks, during which time the patient may also be asked to wear a small device on the wrist. This device, called an activity meter, records movement. In subsequent visits, a thorough physical examination is conducted – if this has not already been done by the referring doctor – as this may uncover clues to important medical disorders relevant to the sleep problem. Attention is also paid to signs of possible psychiatric or psychophysiological disorders. A clinical diagnosis is then made followed by a recommendation for treatment or further clarification of the problem.

For what reasons are patients admitted to the clinic as in-patients?

If the therapeutic program being followed by the patient at home isn't working, we admit the patient for close supervision and carry out additional tests where necessary. With certain illnesses, a period of hospitalization for diagnostic or treatment purposes often can't be avoided. These include sleep apnea, treatment-resistant chronic insomnia, restless legs syndrome, narcolepsy, drug dependence and sleep-wake cycle disorders. However, we make every effort to keep hospital stays as short as possible. For example, the longest admission is 3 weeks for sleeping pill withdrawal. Insomnia patients usually stay 2 weeks.

What happens in the sleep lab?

In the sleep lab, qualified personnel observe the patterns of a patient's sleep during the entire night using polysomnography (PSG). This is a complex procedure in which multiple physiological variables during sleep are continuously and simultaneously recorded. We routinely use 18 different wires to measure these variables (see fig. 1). The picture and sound of a video recording are used as an added check and to assist the interpretation of the data. As a tool, PSG is essential to formulate diagnoses and enhance our understanding of normal sleep and its disorders.

How many patients did you treat in your first year of operation and which sleep disorders were most common?

About 650. Insomnia was the most common disorder and patients fall into two main categories. In the first group are those whose insomnias have psychological causes or are sleep-wake cycle disturbances. Insomnia patients are much more likely to be women and have an average age of around 40. Interestingly, the patients with sleep-wake cycle disturbances are, in our experience, almost always young, often between 16 and 24 years of age. There is much more pressure on younger people these days. The security of the '50s and '60s is breaking down, and instability in society in families, relationships and jobs is taking its toll. The second group comprises patients whose sleep-wake disturbances are due to respiratory problems.

Can you tell us anything about the clinic's success so far, or is it too early?

We consider ourselves to have been successful if patients can sleep normally without the use of medication and are able to have a normal day. What's important is that they are well throughout the day. They may still complain that they wake up occasionally during the night. It's very difficult to determine the actual success rate. For example, with the 300 insomniacs we have treated so far, our success rate is about 70%. But success can be short-lived. Careful follow-up is necessary to evaluate long-lasting benefits, but the clinic is still too young to be able to give you a long-term picture.

The majority of people with sleep problems approach their family doctors first. How well do you think the medical profession is equipped to deal with these patients?

Sleep medicine did not have a place in the traditional curriculum. American statistics show that as recently as 1993–4, the average medical student only received 6–7 hours of instruction on sleep during their studies. This is clearly not enough. Family practitioners often don't have the knowledge, facilities or the time to spend the many hours usually required to adequately diagnose or treat sleep disturbances. There is still the tendency to reach too often for the prescription pad. Although sleeping pills can, in certain circumstances, provide relief for a short time, they lose their effectiveness and may lead to dependency. Most sleep complaints, however, can be remedied with simple measures, so it is important that family doctors are equipped with the information to determine which patients they can help and which patients need to be referred to specialists. All patients, wherever they are treated, require a good explanation of the nature of normal sleep and individualized support throughout their therapy.

Is the situation improving?

As we discover more about sleep, we are learning to diagnose and treat a wider variety of sleep disorders. There are more practitioners entering the field and the amount of material for which a sleep specialist must be responsible has increased both in breadth and depth. However, the number of specialists is still too small to bring the benefits of sleep medicine to all those who need it. Awareness is growing about the importance of sleep and its effect on the human organism and this awareness will surely be reflected in medical education programs and interdisciplinary cooperation. But currently there is still much work to be done.

Dr. Schwander, how can the average person judge the quality of his or her sleep?

The quality of sleep is judged by the day. A person's sleep can be considered sufficient when he or she feels fit and productive during the entire day. Sufficient sleep is very important for a good quality of life. Psychological well-being and the ability to perform on both a physical and mental level are strongly affected by sleeping habits. Refreshing sleep is dependent not so much on its length but rather on its quality. Most adults need 7–8 hours sleep a night in order to feel well rested the next day. However, the amount of sleep required varies with each individual and decreases during the course of life, and sleep becomes less stable.

Finally, Dr. Schwander, do you have a word of advice for the many of us who have trouble getting to sleep?

Certain sleep routines are very important. Very often sleep problems develop from a lack of routine and this often starts in childhood. Try to get up at the same time every day and sleep only as much as you need to feel refreshed. Make sure the bedroom is at a comfortable temperature and free from light and noise. You should reduce liquid intake in the evening and avoid alcohol and caffeine products. Regular exercise during the day is also very important. And remember, the bedroom is a place for sleeping, not for watching TV, having a cigarette, or worrying about what you didn't do during the day. Don't take your problems to bed!

Jürg Schwander trained as an internist specializing in endocrinology and metabolic diseases and has gained extensive clinical experience both in Switzerland and overseas. He was head of the emergency room of the University Hospital in Basel before entering the field of sleep medicine in 1992. In 1995, he established the Clinic for Sleep Medicine in Zurzach.

A Glossary of Sleep Disorders

Snoring and Sleep Apnea
Snoring is usually no more than an annoying habit, but can be a symptom of a severe sleep disorder: sleep apnea. People suffering from this syndrome stop breathing for a short time (at least 10 s), wake up briefly to gasp for air (without being conscious of it), and fall back to sleep. Such episodes can occur more than 100 times a night. As sleep is broken up into small pieces, there is no deep sleep. The consequences are tiredness and a reduced ability to perform during the day.

Insomnia
Difficulties in falling asleep or sleeping through the night can have many different causes. These can be of a psychological nature (e.g. chronic depression, acute stress), relate to surroundings (e.g. noise, light, warmth) or have a physical cause (e.g. chronic respiratory problems, restless legs, strong pain). Lifestyle and misuse of sleeping tablets are other frequent causes of poor sleep.

Sleep-Wake Regulation Disorders
If the normal sleep-wake pattern is disturbed, it can be difficult for many people to find a sleep-wake rhythm suited to their sleep needs and social situation. This disturbance can be caused by e.g. shift work or frequent flying through time zones. An inability to sleep at night or tiredness during the day can be the consequences of changes in sleep-wake rhythm.

Narcolepsy
People who involuntarily fall asleep during the day and/or have muscular weakness when they are surprised, angry or excited could suffer from narcolepsy. Narcoleptics often have frightening dreams or hallucinations as soon as they fall asleep. The first signs of narcolepsy usually appear in childhood – without being recognized as such – and negatively affect the education and later job prospects of the person concerned.

Restless Legs Syndrome
People suffering from involuntary leg (and more rarely also arm) movements during sleep can wake up repeatedly throughout the night. Because their sleep is so frequently interrupted, sufferers do not get enough rest and often feel excessively sleepy during the day.

Parasomnias
A. Nightmares, bedwetting, sleep walking and talking occur frequently in childhood and usually disappear in adolescence. Investigation is necessary if such episodes persist into adulthood or occur for the first time in an adult or adolescent.
B. Teeth grinding, movement disorders in REM sleep, and epileptic attacks that only occur in sleep are all disorders that require investigation and treatment by specialists.

David N.F. Fairbanks, Washington, D.C.

Snoring

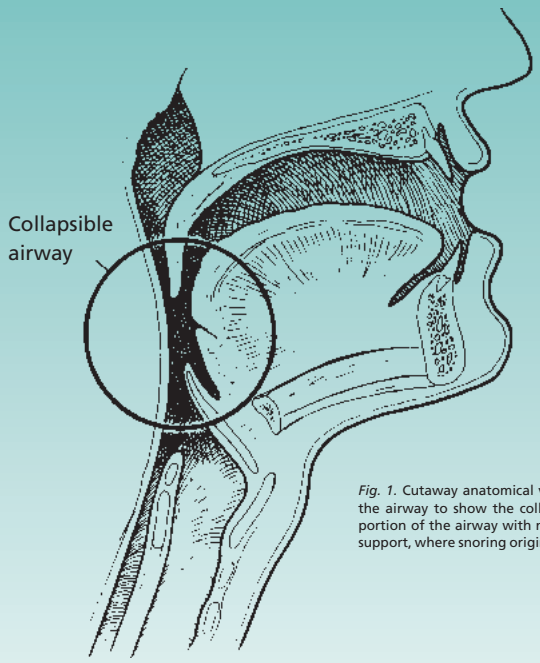

Fig. 1. Cutaway anatomical view of the airway to show the collapsible portion of the airway with no rigid support, where snoring originates.

Snoring – obstructive breathing during sleep – is one of the most prevalent of obnoxious human habits. In 30- to 35-year-olds, 20% of men and 5% of women snore, at age 60, 60% of men and 40% of women are habitual snorers. It is not known why more men snore than women, but an old legend claims that men defended their women at night by making terrifying noises to frighten away beasts of prey.

Snoring is almost exclusively a human trait. 'Wild animals do not snore,' wrote Immelmann, the German naturalist. 'They sleep either in the ventral position or on the side so that the lower jaw is always somehow sustained, thus preventing its falling back.' However, when our ancestors started sleeping on their backs, they became snorers. Most animals do not sleep on their backs, so they do not snore. But bulldogs (and other brachycephalic dogs) snore terribly and often require surgical resection of the soft palate and uvula to keep them from strangling while asleep.

Snoring pays scant heed to the boundaries of social (or political) class. According to H. Dugan in a 1947 article entitled "Bedlam in the boudoir," 'Twenty of thirty-two Presidents of the United States are proved or believed on a thick web of circumstances to have been nocturnal noisemakers in the White House. The list is bipartisan and consoling.' President Theodore Roosevelt once snored so loudly in a hospital that complaints were filed by almost every patient in the wing where he was recuperating. A dictionary of distinguished snorers would be a hefty book indeed: the historian Plutarch said that the Emperor Otho snored; so did Beau Brummel, the Regency dandy; according to the memoirs of ladies who knew him, Mussolini was an astounding snoring artist, and Winston Churchill was a 35-dB snorer, on the account of one naval officer who had the Prime Minister aboard his ship in 1944. But the dubious honor of entering *The Guinness Book of World Records* as the world's loudest recorded snorer goes to the 44-year-old Swede Kåre Walker, for whom peak levels of an astounding 93 dB were measured at Örebro Regional Hospital on May 24, 1993.

The Social Effects of Snoring

Snoring may be a minor annoyance in some households, but in others it disrupts family life, making the snorer an object of ridicule, and committing other household members to sleepless nights filled with resentment. Hapless bedpartners become obsessed with plotting strategies to get to sleep – sleeping pills, ear plugs, ear muffs, pushing the snorer out of bed.

The history books tell us that John Wesley Hardin, a legendary Texas gunfighter of the American frontier, became so upset with the loud snoring of a guest in an adjacent hotel room that he shot through the wall and killed the poor fellow. It is quite possible that many spouses have contemplated similar drastic action. At least one carried out her designs. On December 3, 1983, Dallas police took into custody a woman who 'grabbed a pistol from under her bedcovers and fired five shots,' killing a man 'who snored too loudly.'

The hardships imposed by snorers on their partners are various and distressing. Snorers drive their companions from the bedroom, have friends who will not marry them until the problem is cured, are made the butt of family jokes, and fall asleep driving, watching TV, eating dinner, and while talking to their spouses. Although some people can easily fall asleep in a noisy environment, others cannot, and the noises of snoring are particularly difficult to ignore because of their inherent irregularity. Listeners have been known to lie awake for hours simply marveling at the variety of sounds produced by a snorer, some of which are so frightening they suggest each breath may be the last.

Pathophysiology of Snoring

Snoring is one sign of a number of different disorders. The sounds of snoring originate in the collapsible part of the airway where there is no rigid support, from the epiglottis to the choanae (fig. 1). It involves the soft palate, uvula, tonsils, tonsillar pillars, base of the tongue, and pharyngeal muscles and mucosa. Four factors, singly or in combination, contribute to snoring.

(1) In most adult snorers, the cause lies in incompetent tone of the palatal, lingual, and pharyngeal muscles. Consequently, in deep-sleep stages, the muscles fail to keep the airway open during inspiration. The tongue falls backward into the airway and vibrates against the flaccid soft palate, uvula, and pharyngeal tissue. The effect is exaggerated if the snorer has consumed alcohol, sedatives, tranquilizers, or antihistamines before going to bed. Hypothyroidism and some neurological disorders also contribute to poor muscle tone and hence snoring. Unfortunately, inadequate muscle tone is often not very apparent on physical examination of the awake patient. However, a characteristic finding in some patients are redundant vertical folds in the tissues of the posterior pharynx, making it look more like an intestine than an airway.

(2) Space-occupying masses impinging on the airway can contribute to snoring. In children, snoring is almost always from enlarged tonsils and adenoids, and a third of adults have tonsils large enough to contribute to the airway problem. A receding chin may be unable to keep the tongue sufficiently forward, while Down's syndrome and acromegaly produce absolute tongue enlargement. Cysts and tumors are occasionally the cause of snoring.

(3) An excessively long soft palate and uvula will decrease the anterior-posterior dimension of the nasopharyngeal airway and vibrate during respiration.

(4) Restriction of the airflow into the nose increases the negative pressure during inspiration which draws together the flaccid tissues in the collapsible part of the airway, where they vibrate and cause snoring. It is a common observation that many nonsnorers may start to snore when they have a cold or an allergy attack.

Obstructive Sleep Apnea

The most advanced stage of snoring is obstructive sleep apnea (apnea comes from the Greek term meaning 'want of breath'), which can cause profound cardiac, pulmonary, and behavior problems.

Whereas snoring means partial obstruction of the airway, apnea means total obstruction. The snoring is interrupted by episodes of silence during which the sleeper struggles unsuccessfully to breathe. After a few seconds, the sleeper snorts loudly as he or she awakens briefly to force open the airways and resume breathing. This is often accompanied by kicking or flailing of the arms, or a total body spasm. The half-awake victim may rise up in bed or fall out of it entirely. Such behavior invariably drives any companion to different sleeping quarters.

Occasional brief obstructive events are harmless and quite common in the normal adult population. However, it is considered pathological when apnea episodes last for more than 10 seconds and occur more than seven to ten times an hour. Many apnea patients may be obstructed for over 30 seconds at a time, suffer hun-

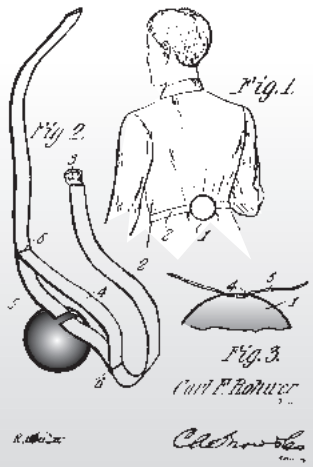

Fig. 2. Snore Ball – a remedy designed to keep snorers from sleeping on their backs.

There ain't no way to find out why a snorer can't hear himself snore.

Mark Twain

dreds of such episodes in a night and spend over half their sleep time in total airway obstruction.

The consequences for such patients who must repeatedly arouse themselves to lighter sleep stages just to breathe are serious. Not having enjoyed sufficient deep-stage sleep they will get up in the morning feeling unrefreshed and, chronically sleep deprived, they will feel sleepy throughout the day. They may fall asleep while working, driving, reading, or having conversations.

The hypoxemia resulting from chronic sleep apnea leads to predictable cardiovascular effects. Hypoventilation results in pulmonary hypertension, then to an increased cardiac work load and to systemic hypertension in at least 50% of patients. Significant aberrations occur in blood oxygen and carbon dioxide levels, and cardiac arrhythmias appear in almost all such patients and probably account for the sudden death in bed of 2,000 to 3,000 patients each year in the US.

Children with massively enlarged tonsils and adenoids are at risk for significant cardiovascular, developmental, educational, and behavioral consequences of snoring and sleep apnea syndrome. Sleepiness in children is often manifested as hyperactivity or antisocial behavior.

The Treatment of Snoring

There is no lack of would-be snoring remedies – the US Patent and Trademark Office has a list of over 300. Some are variations on the old idea of taping a marble on the snorer's back to force sleeping on the side (fig. 2). Chin straps to keep the mouth closed and whiplash-neck sprain collars to keep the chin up are usually disappointing as snore cures. Nasopharyngeal tubes and mouth inserts to pull the tongue forward have been reported as successful, but understandably patients are reluctant to wear such uncomfortable devices. A number of ingenious electronic gadgets have been devised which deliver painful or unpleasant stimuli to patients when they snore, as if they could be trained or conditioned, Pavlovian style, to desist. But since snoring is a purely involuntary phenomenon, if these devices work, it is most likely because they prevent the snorer from going to sleep altogether.

For adults who are mild or occasional snorers, the self-help remedies listed in table 1 are worth trying. Tricyclic antidepressants are helpful to some snorers. Protriptyline, for example, decreases the amount of time the sleeper spends in rapid eye movement sleep, which is when snoring and apnea are at their worst. However, the side effects of stimulating and mood-elevating drugs may be intolerable: insomnia, prolonged dreaming with nightmares, constipation, urinary retention, altered sexual potency, and aggravation of cardiac arrhythmias. And even if the medications are effective, taking them for a lifetime may be far from desirable.

Surgery can correct nasal obstructions and can also remove and tighten up redundant pharyngeal tissue and shorten a long, floppy uvula and soft palate. This operation, known as uvulopalatopharyngoplasty is remarkably successful in the treatment of 'obnoxious snorers' and many obstructive sleep apnea patients. Tracheostomy (opening the trachea) is the ultimate treatment for patients with far-advanced and life-threatening sleep apnea, but both patients and spouses may find the appearance, the sounds, and the care of a tracheostomy somewhat objectionable.

Snoring and obstructive breathing are never normal in children. If no other specific cause for the snoring is discovered, tonsillectomy and adenoidectomy will usually bring dramatic relief and make an important difference to the child's health and well-being.

Table 1. Self-help suggestions for snorers

- Adopt an athletic lifestyle and exercise daily to develop good muscle tone and to lose weight.
- Avoid alcohol within 3 hours of going to bed.
- Avoid tranquillizers, sleeping pills, and antihistamines before retiring.
- Sleep on one side rather than on the back.
- Tilt the entire bed with the head upwards.
- Try wearing a whiplash collar at night to keep the chin extended, and avoid using a thick pillow that will kink the neck.
- Drink a cola or cup of coffee before going to bed so that the partner can get to sleep first (although the snoring may be worse when the stimulant wears off!)

Conclusion

An anonymous wit once said, 'Laugh and the world laughs with you. Snore and you sleep alone.' Snoring is not funny to those whose lives are severely disrupted by this extremely prevalent breathing disorder. It can lead to serious medical problems and is a significant impediment to good interpersonal relationships. It should be neither ignored nor belittled, but fortunately, with today's expanded medical understanding, and a wide variety of possible approaches to its treatment, snoring is not helpless either.

Acknowledgement

Figures 1 and 2 are reproduced with permission from: Fairbanks DNF, Fujita S, Ikematsu T, Simmons FB (eds): *Snoring and Obstructive Sleep Apnea.* New York, Raven, 1987, pp 9, 3.

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Karger Gazette

Published by S. Karger AG, Basel
Edited by Anne Blonstein, Dagmar Horn and Robyn Stewart
Design by Erich Gschwind

Printed on recycled paper

Hypnos, the god of sleep.

This head fragment is a rare bronze from the late classical period in Greece (4th century BC). The British Museum, London.

Bettina Eichin: **Sleeping Muse** *(bronze, 1982).*

Bettina Eichin was born in Bern, Switzerland, in 1942. Having decided at an early age to become a freelance sculptor, she began training in 1960 as a stonemason and sculptor, first in Thun and later in Bern. Extended visits to Israel and Greece gave new impetus to her artistic development. Since 1979, she has lived and worked in Basel and is best known for her sculpture Helvetia on Her Journey, *commissioned by the city of Basel and located prominently on one of the old bridges spanning the Rhine. Her prime interest is art in public spaces and her monumental bronze figures are created to provoke an interactive response to the work within its specific location. The sculpture depicted on the front and back pages of this issue of the Gazette can be seen in the French garden in Wenkenpark, Basel.*