

“Every night and every day,
the intolerable clarity of insomnia
had weighed upon him”

JORGE LUIS BORGES,
Labyrinths



Wide awake

Lack of sleep activates sexuality, increases the sensitivity to pain and damages the liver and the heart

RICARDO ZORZETTO

PHOTOGRAPHS BY HÉLIO DE ALMEIDA

Published in April 2005

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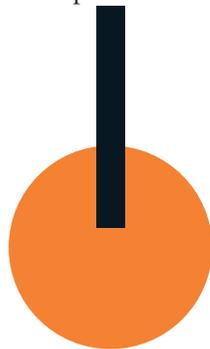
Monica Levy Andersen knows very well the importance of a good night's sleep. Even so that she sacrificed hours of precious sleep during months and months in order to dedicate herself to her recent passion: to investigate how long periods of sleep deprivation affects the human organism. From October of 2002 until February of 2003, researcher Monica got up from Monday to Saturday at 5:30 am and before seven o'clock she was already in her laboratory with dozens of rats preparing for the first experiments of the day. In a small room of the Sleep Laboratory of the Federal University of São Paulo (Unifesp), this biomedical researcher accompanied, during these months, the behavior of rodents kept awake for four days in a row. Her initial goal was to investigate the origin of their aggressiveness and agitation from the lack of sleep, observed for the first time at the end of the 70s by the medical doctor Sergio Tufik, today one of the main specialists in sleep disturbances in the country. At the head of the Sleep Studies Center, Tufik is coordinating a series of research studies that are mapping out sleep disturbances, capable of bringing about damage to the neurons and to organs such as the liver and the heart.

Monica observed an unexpected effect that — at first appearance—could excite young men, as well as question the current knowledge surrounding sex hormones. After having taken the rats from inside a tank with water in which the rats balanced themselves upon dry platforms — if they were to fall asleep they would fall into the water and awake — and transfer them to their individual cages, she noted that half of the animals had a spontaneous erection and ejaculation before falling asleep, even without any female rat close by. “As sleep deprivation affects the working of an area of the central nervous system associated with pleasure, I found in this effect the opportunity to evaluate if drugs such as cocaine, marijuana, and amphetamines improve sexual performance as their users have claimed”, says Monica.

And did it improve? It depends. Called hyper-sexuality, this increase in interest for sex became even more intense when the biomedical doctor injected cocaine or ecstasy into the rats, drugs that act upon the pleasure center of the central nervous system. All of the animals that received one of these two compounds had an erection — in many cases there were multiple erections. Before some imprudent big grown up boy attempts to repeat this experiment, one needs to make it clear that this effect is apparently only of temporary benefit. The continued use of cocaine causes sexual impotence and the prolonged deprivation of sleep generated a biological imbalance in the organism capable of leading to death.

The in-depth study of this effect has rendered to thirty-one-year-old Monica enviable scientific production. There are some thirty four scientific articles, twenty of them already published and the remainder to come out soon, all surrounding her doctorate thesis of 500 pages written over a three year period with funding from FAPESP. This work may permit her to arrive at a possible explanation for this hyper-sexuality in the face of the forced sleep deprivation: they would be a type of compensation for the erections that occurred during sleep that the rat did not have whilst it

remained awake. Some mammals, amongst them rats and male human beings, have spontaneous erections in the most peculiar of the five phases of sleep the REM (Rapid Eyes Movement) sleep, when the muscles associated with voluntary movement remain paralyzed and when dreams occur.



In this phase the central nervous system finds itself as active as when the subject is awake, which is the reason why the REM is also called paradoxal sleep (up until eighty years ago it had been thought that the brain activity was less intense during sleep). Some five years ago the medical doctor Markus

Schmidt, from the Ohio Sleep Medicine Institute, in the United States, proposed that these erections, associated with REM sleep, had a biological function: they served as training for copulation, since, at least in nature, survival depends on efficient reproduction and encounters for mating are unpredictable. Therefore, one needs to be prepared.

These indications led Monica and her work supervisor Sergio Tufik, to think about hyper-sexuality as a second effect of the same cause: just like the person who does not close their eyes for an entire night needs more sleep hours the following morning — this is the so-called sleep rebound—, the same thing happens with the spontaneous erections of REM sleep. The most important point in this series of studies is to indicate that an imbalance in the levels of chemical messengers of the central nervous system — the example of the neurotransmitters dopamine and serotonin, upon which react cocaine and ecstasy respectively—is associated to erectile dysfunction of neurological origin. Set in motion by the alteration in the rhythm of liberation of these neurotransmitters in the regions of the encephalon linked to sexual desire and emotions, this form of erectile dysfunction is different from that of physical origin, brought about by insufficient blood irrigation of the penis. “Possibly desire and sexual performance depend upon all of the neurotransmitters being found at adequate levels within the central nervous system”, the researcher says.

Progesterone and erection - Through the blood analysis of the animals, Monica made another intriguing discovery, capable of influencing the therapies for erectile dysfunction in human beings. She verified a brutal reduction in the blood levels of the hormone testosterone. Found in concentrations twenty times greater in males than in females, this hormone is generally associated with sexual desire and an erection. Four days after the beginning of the experiment there was a decline of around 90% in the level of testosterone in the non-sleeping rats, whilst the levels of the hormone progesterone, responsible for the preparation of the uterus for the implantation of the fetus and for the development of the mammary glands during pregnancy showed a level five times above that expected.

Had the deprivation of sleep, therefore, brought about a type of pregnancy in the male rats? Clearly not. Monica believes in a redefinition of the roles. The progesterone hormone would be performing in the masculine organism a function previously attributed to testosterone, to allow for a penis erection, whilst the testosterone would respond to the intensity of the libido. In search of confirmation, Monica gave on its own testosterone, progesterone or estradiol to distinct groups of rodents, which had gone through four days without sleep and then had received cocaine — different from previous studies, these animals had been castrated and their organisms practically no longer produced these hormones. Treatment with progesterone brought about an erection in six out of every ten rats, whilst testosterone brought about the same effect in 30%, according to the article

THE PROJECT

Sleep Studies Center

MODALITY

Research, Innovation
and Diffusion Center (Cepid)

COORDINATOR

SERGIO TUFIK – Unifesp

INVESTMENT

R\$ 13,121,912.69 (FAPESP)



“I spent a miserable night, full of frightening dreams, of terrible visions”

WILLIAM SHAKESPEARE,
Richard III

published in 2004 in the *Journal of Neuroendocrinology*.

It was yet one more indication that progesterone would perform an important function in erection. However, the counterproof was lacking. In a similar study, Monica gave to the animals a compound called mifepristone, which annuls the effect of progesterone. The animals that received mifepristone did not have an erection, according to the article published this month in *Hormones and Behavior*. “Before this study there were no scientific reports concerning the role of progesterone in an erection”, says Elaine Hull, from Florida State University in the United States, a world authority in the neurophy-

siology of sexual behavior. In Elaine’s opinion, that fact that the dose of progesterone that showed itself to be effective had been very high—the rats received 100 milligrams per kilogram of body weight, a level some 250 times higher to that used in order to leave the rats used to copulation—does not exclude the participation in the erection of another hormone such as corticosterone, associated with stress. “Even at that, it is an interesting effect, since as yet the action of neither progesterone nor corticosterone have been demonstrated in the control of an erection”, says Elaine Hull.

Before young men resolve to rob the anti-conception pill of their girlfri-

ends based on progesterone, one needs to make two points very clear. Not always do the effects observed in rats happen in human beings. “These results don’t mean that a normal man will have an erection if he takes progesterone”, says the physiologist Janete Franci, from the University of São Paulo in the city of Ribeirão Preto, who is studying the physiology of reproduction in rats. Specific studies are necessary in order to prove the role of progesterone in an erection, since the rats evaluated by Monica did not find themselves in a normal physiological state. “These studies reopen the question of the influence of this hormone in masculine sexual behavior”, says Janete.

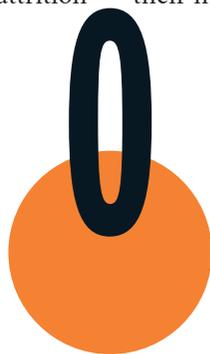
“This is one of our main contributions in order to understand the damages caused by the deprivation of sleep”, says Sergio Tufik. As well, he began to study the consequences of fewer hours of sleep upon the organism some twenty-five years ago, after having obtained an unexpected result in an experiment. Under the guidance of the psychopharmacologist Elisaldo Carlini, from Unifesp,

Tufik was investigating the effect of drugs such as marijuana upon the central nervous system when he verified that the deprivation of REM sleep brought about a chemical imbalance and made the nerve cells more sensitive to the action of dopamine. Tufik, Carlini and the pharmacologist Charles Lindsey published in 1978 this resulted in an article in *Pharmacology*, which turned itself into a reference in this area. This discovery re-directed Tufik’s work, a man of almost two meters in stature and of deep voice, who coordinates around sixty researchers in the largest sleep investigation center in Brazil, with an average of twenty five scientific papers published per year.

Obesity and apnea - The investigation into the exaggerated sexual behavior of rats is what mostly catches the attention, but it is a long way from being the only relevance concerning the effects of lack of sleep, which affects almost one third of the population—around 60 million Brazilians. Other studies with animals and human beings are helping to produce an understanding of how factors apparently unrelated to sleep—such as the chronic pain of arthritis or the emotional attrition of an argument at work—affect the quality of sleep, weaken the performance of memory and make us take a nap the following day.

Research from the Unifesp team is helping to improve the night rest of those who do not sleep well because of brief interruptions in their breathing—apnea—during their sleep. Generally, caused by an obstruction of the air passage to the lungs and worsened by obesity, apnea is a problem for between 2% and 4% of people older than forty and increases by four times the risk of deve-

loping arterial hypertension. The accumulation of fat, especially around the neck, elevates the risk of the occurrence of breathing failure among men, according to research coordinated by the lung doctor Sônia Togeiro, carried out with one hundred obese patients of both sexes. Among women, the probability of developing apnea increases according to the increase to the level of their body mass, a number obtained by dividing their weight by the square of their height.



ne of the main treatments for obstructive sleep apnea is the use of a mask linked to a piece of apparatus that maintains the flow of air to the lungs, known by the acronym CPAP. A study by the lung doctor Lia Bittencourt has shown that sticking to the CPAP was greater when the user had gone through a guidance program about using the apparatus.

The rheumatologist Suely Roizenblatt has recently proven that the relationship between pain and the quality of

sleep is a two-way street: pain can well upset sleep, but alterations in sleep also appear to increase sensitivity to pain. In both cases, the result is always an intense sensation of tiredness during the following day, even if the person has slept for a sufficient number of hours to recharge their energy. By way of polysomnography — an examination that measures the brain's electrical activity, heart beat and respiration when a person is asleep—, Suely compared the standard of sleep of seventeen healthy children with that of thirty four with fibromyalgia, a problem of unknown origin that cause pains disseminated by muscles or bones, as well as fatigue. During the interview with the patients suffering from fibromyalgia, the researcher noted that many mothers complained that they could not sleep well and she decided to include them in her study. The result: 71% of the mothers of children with fibromyalgia had also displayed this same problem.

The analysis of the polysomnographs revealed a disturbance in deep sleep, also called the sleep of the slow waves, which precedes REM sleep. “These subtle alterations do not modify the

A long way from heavy medicines

A watershed in the clinical research carried out at the Sleep Institute of Unifesp has been contributing to an improvement in the quality of life of people who every night need to count flocks of sheep before going off to sleep. In a study that demanded a certain amount of audacity, the neurologist Dalva Poyares showed that it is possible to leave to one side the medicines used to induce sleep. She proposed to a group of twenty-five patients with chronic insomnia that they abandon all of a sudden the benzodiazepines that they had been taking for at least two years. It is estimated that one in four insomniacs take this medicine that doctors avoid prescribing as it generates dependency.

The idea went well. After some days the ex-users of benzodiazepines managed to fall asleep without taking anything. To be fair, on the first day without the medicine the insomnia got worse and the volunteers suffered even more before sleeping. But after three days of lack of sleep and of the nervousness caused by the withdrawal symptoms from the medicine, they diminished and the patients managed to sleep better. The polysomnographs revealed that, two weeks after abandoning the medicine, the quality of the sleep of these individuals was already better than when they had been taking the medicine. The reason is that benzodiazepines diminishes the duration of the sleep phases 3 and 4, those that are most energy restoring, in accordance with the study's results published during 2004 in the *Journal of Psychiatric Research*. “The effects of insomnia are not as serious as those brought on by the chronic use of benzodiazepines”, says Dalva. As insomnia comes back after two weeks without the medication, the way out is to look for alternatives that are more appropriate for prolonged usage, whose indication varies from case to case.

“ Oh, Dream, in which all find rest,
the most pacifying of Gods, who calms the mind... ”



OVIDIO,
Metamorphosis

distribution of the sleep phases, but affect their quality”, explains Suely. It becomes clearer to understand what she had discovered after a rapid explanation of the structure of sleep, which is characterized by a REM stage and another non-REM stage, with four other phases. When the eyes begin to get heavy after a long working day, it is a sign that the brain is changing its working rhythm and is beginning to slow down. In this phase of drowsiness the frequency of the brain’s electrical waves diminishes, consciousness drifts away and the muscles relax. But any noise still upsets and awakens. This is phase 1 of sleep, which lasts a few minutes. In phase 2, the standard of waves is again altered and the electroencephalogram registers rapid electrical discharges, of less than a second in duration. The

Without nodding off on the highway

Over a period of five years, the team headed by Marco Túlio de Mello, from the Sleep Institute, has collected the results in the reduction of accidents brought about by sleepiness, the cause of between 30,000 and 50,000 deaths on Brazilian highways. In 1995 Mello began to defend the need to reorganize the working hours of professions drivers, based on interviews that he did with some four hundred bus drivers. In their replies, 16% of them assumed the fact that they had fallen asleep at the wheel. “Has some friend of yours nodded off while at the wheel?”, and the number of affirmative replies jumped to 52%.

During 2000, the bus company from the state of Minas Gerais, Nacional Expresso sent two hundred and thirty drivers for a polysomnograph test. The

result: 55% of them felt sleepiness at the same hour during which they should have been driving. Mello proposed a work timetable that followed the biological rhythm of the drivers, who today alternate their shifts only once per month and no longer after every thirty-six hours. The number of monthly accidents fell by 40% and the costs due to minor accidents went down from R\$ 150,000.00 to R\$ 30,000.00.

Last year it was the turn of Reunidas Paulista, from the town of Araçatuba, in the interior of São Paulo State, to evaluate their four hundred motorists. Rescheduling the scale of the shifts, the number of fatal victims on one of the company’s routes fell from 3.6 to 0.6 for every 100,000 kilometers driven. There was as well a reduction of up to 30% in the accidents during the critical hours—between three and five o’ clock in the morning and between one and three o’ clock in the afternoon. The effect of this research could even be much wider as the National Transit Board is studying the possibility of making the evaluation of professional motorists sleep by way of polysomnographs obligatory with each renewal of their driving license.

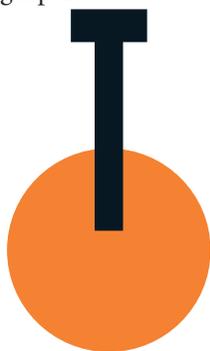
body has already become relaxed and it is more difficult to awake. These two initial phases are given the name of light sleep or sleep of rapid waves and lasts around forty five minutes, half of a complete sleep cycle.

Alpha effect - As the sleep deepens in phases 3 and 4, the brain waves get progressively slower. The breathing rhythm falls, the heart beat rate declines and noises no longer upset the rhythm. "This is when it becomes more difficult to waken up", explains the English biologist Paul Martin in *Counting Sheep: the Science and Pleasures of Sleep and Dreams*. It is within these phases, considered to be the most compensating of all of the sleep cycle, that these tenuous alterations known as the alpha pattern come about.

There is as well an association between the occurrence of the alpha pattern and the increase of intensity of pain after sleep, as another study showed, carried out with forty women with fibromyalgia and forty-three without the problem. In Suely's opinion, this interference called alpha pattern can prejudice the production of serotonin. Generally produced during the 3rd and 4th phases of sleep, serotonin acts as a neurotransmitter in the central nervous system, but produces an analgesic effect in the peripheral nerves. "This alteration of sleep appears to reduce the resistance to pain", the researcher comments. As a consequence, any kind of pain—stubbing one's toe on the end of a table, for example—is always felt with more intensity. The use of ultrasound in the treatment of fibromyalgia showed itself to be efficient in reducing the pain, but did not eliminate the interferences in the sleep of the slow waves of these patients, according to a study done by Suely and Tatiana Almeida published during 2003 in the journal *Pain*.

A comparison of the sleep of twenty healthy children and adolescents between the ages of ten and sixteen with that of twenty one young people of the same age group suffering from rheumatoid arthritis, an inflammation that makes the joints rigid and painful, suggests the opposite to that observed with

fibromyalgia. Suely did not find any interference in the sleep of the fast waves not with the slow waves, but the polysomnography pointed to 12% of the children and adolescents with arthritis awakening during the night after having fallen asleep, which normally occurs with 2 % of those without inflammation of the joints.



The sleep of the young with arthritis was also of inferior quality, with more awakenings or interruptions in the different phases of sleep. They woke up around twelve times per hour of deep sleep and twenty four times during light sleep and REM sleep, whereas these awakenings were no more than three per hour of sleep for those without a problem in their joints. The result of this awake-sleep-awake-sleep is that the person gets up with the same feeling of tiredness that was there before sleeping.

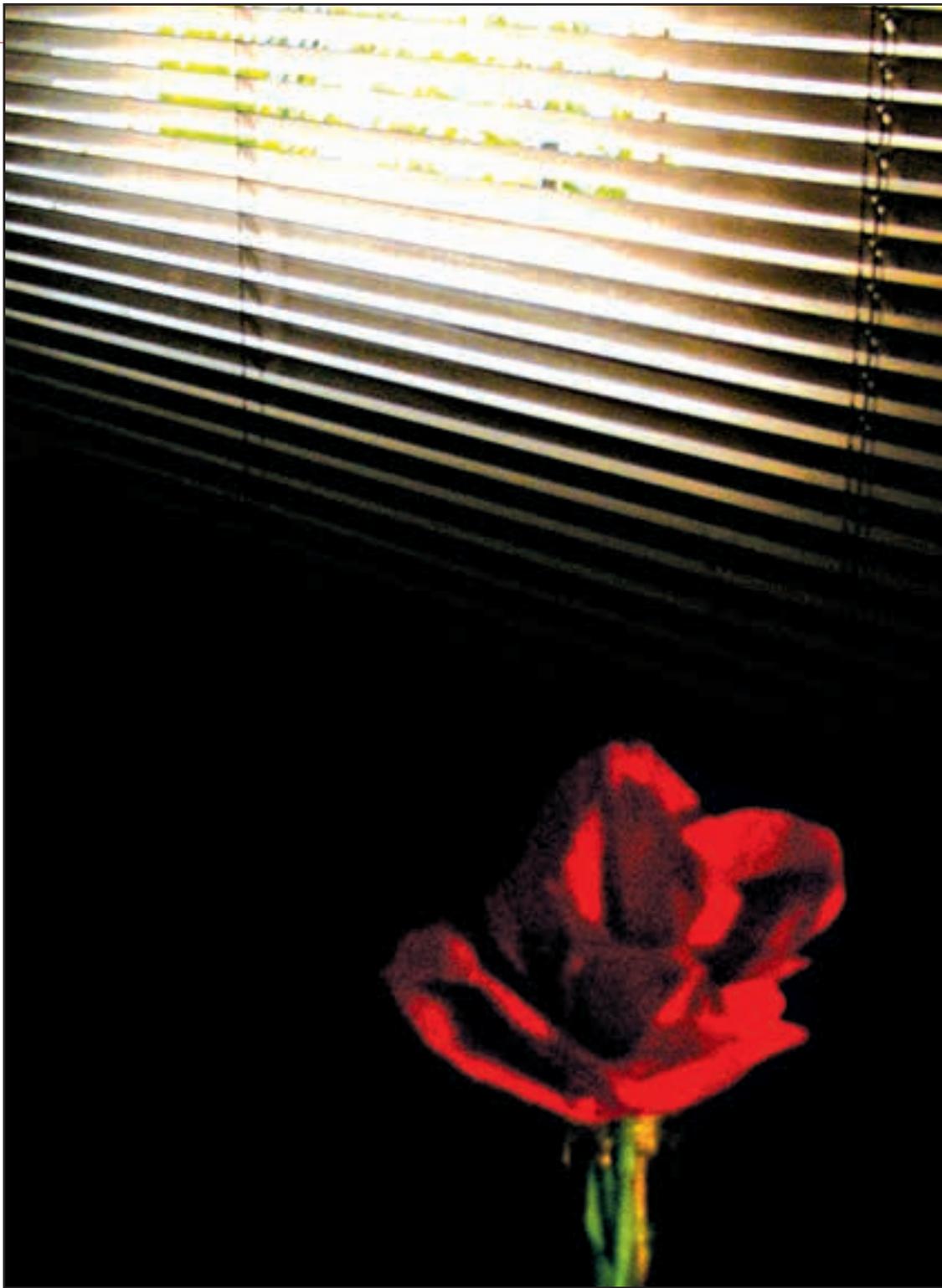
Another team from the Sleep Laboratory, headed by the biomedical doctor Deborah Suchecki, is beginning to uncover how weariness from a tumultuous day robs the possibility of a good night's rest. One of the first analyses has shown the awakening affects causes by acute psychological stress, as would be brought on with the discovery of an unexpected debt in a bank account. Deborah submitted rats to different forms of stress with the objective of investigating if they were to produce distinct alterations in sleep. In order to induce the animals into this state, she left a group of rats immobilized for an hour before the time at which they would normally sleep and afterwards registered the standard of sleep.

Instead of falling into sleep, the rodents found themselves to be alert and practically none of them slept during the first hours after stress. After, compensating the lost hours during daylight, the rats extended their sleep for almost three hours. This result helped to understand why people remained sleepless the day following that in which they had confronted a stressful situation, such as being assaulted in the street. Deborah obtained similar results when she submitted the laboratory animals to physical stress, exposing them to a

cold temperature of 4°C for an hour. The explanation: during stress the organism responds with a faster liberation of corticoids, hormones that accelerate the production of energy and help to maintain the body alert. But the corticoids become harmful when they remain at high levels for a long time.

There are indications that the damage done through lack of sleep really goes beyond tiredness that does not go away and the difficulty of concentration during the day after. A bad night's rest echoes through all of the body. In 1997 the biologist Vânia D'Almeida observed the first signs that sleep deprivation could well bring about lesions in some organs. In a series of studies with rats that slept less than normal, Vânia noted a reduction of the chemical compound responsible for the elimination of the organism's free radicals—glutathione—in the hypothalamus, an area of the central nervous system associated with the regulating of the body's temperature, with hunger and with the cycle of sleep and vigil. It is not yet clear if the reduction in the level of this anti-oxidant truly favors the death of the hypothalamus cells, but last year the pharmacologist Roberto Frussa Filho discovered how sleep deprivation affects memory: the accumulation of free radicals generated by sleepless nights damages the nerve cells of another region, the hippocampus, reducing the capacity of retaining information over a long period, in accordance with the study published in 2004 in the journal *Neuropharmacology*.

The liver and the heart also suffer. Vânia verified that, in the liver of rats that had suffered sleep deprivation, the production of proteins typical of an acute inflammation such as fibrinogen and the protein C-reactive, also associated with a higher risk of cardiac problems, had increased. Up until this moment the results are pointing towards the prolonged absence of rest elevating the consumption of the organism's energy, which generates an attrition of the liver similar to that brought about by the exaggerated consumption of alcoholic drinks. As well there are signs that, with fewer hours between the sheets, the cardiac muscle brings about alternative forms of obtaining energy in response to this extra attrition. •



**“ God bless the inventor of sleep, the cover
that covers men’s thoughts... the weight that
levels serves one like a king and
the simple one like a wise man ”**

**MIGUEL DE CERVANTES,
*Don Quixote***