Sleep

Health and Sleep
Un voyage à travers les grandes découvertes et les promesses portées par les sciences du vivant au xxie siècle,

*sous la direction de* Catherine Jessus

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Lack of sleep: watch out!

The alarm has been raised for more than ten years, but things are getting worse. We of the modern world do not get enough sleep. Both young and old, we demote sleeping to the bottom of our priorities. Not just below performance and work but even behind leisure activities. Consciously or not, we ignore the—often serious—consequences of insufficient sleep on our mental and physical faculties, and on our health. A real public health problem, lack of sleep is also a social issue because in an era of new information and communication technologies, we are living a round-the-clock life seven days a week. The result is that we do not set aside either enough time or space free of external stimulation, an essential condition for "good" sleep. A hyperconnected civilization with a social life that encroaches deep into the night, putting off the time we go to bed but not the time our alarm clock goes off. Furthermore, the virtues of getting up early are extolled, but less emphasis is put on the corollary fact that this means going to bed earlier in order to ensure enough sleep. Finally, the focus on "well-being"—another performance contest—is intensified by the world of connected objects and their manifold applications. It is important to point out that none of these are capable of analyzing sleep—contrary to what their designers claim. Given this proviso, they can be of use when it comes to recoding physical activity and daily rhythms, thus providing information about the effects of daily habits on sleep and therefore, the impact of this important factor on health.
We spend one third of our lives asleep. Sleep appears to be essential for proper physical recovery. Recent findings also demonstrated that it is an essential part of the learning process. But what happens inside our brains after we fall asleep? The 17th National Sleep Day organized on 17 March 2017 by the Institut national du sommeil et de la vigilance (INSV, National Institute of Sleep & Vigilance) gave Science&Santé the chance to learn about the latest discoveries that are steadily lifting the veil on the roles of different types of sleep, be it light, deep or rapid eye movement sleep. An opportunity to understand the repercussions—both short-term and long-term—of poor sleep on our health.
On at least one point, the picture is reassuring: the average time spent sleeping by French people has stabilized. After a long, apparently inexorable decline, it seems to have now bottomed out at an average of 7h05 during the week and 8h10 at the weekend, according to a 2016 survey conducted by the Institut national du sommeil et de la vigilance (INSV, National Institute of Sleep & Vigilance) on a representative sample of the active French population. These figures have changed little over the last five years and are now within the normal range in developed countries. Nevertheless, in just half a century, the time devoted to sleep every night has decreased by one-and-a-half hours. And annual INSV polls only confirm that the French do not sleep enough.

"Most adults need to sleep for at least eight hours a night. Although needs vary from one person to another, it isn’t the time itself that indicated the need for longer sleep but rather the difference between week days and weekends”, explains Joëlle Adrien, President of INSV.

"Surveys have shown that, globally, the French do not sleep enough given that they need an extra hour at the weekend to catch up.” And for many people, sleep debt is a particular problem. One in four French people claim they sleep less than six hours a night on work days, a deficit that results in their sleeping an hour-and-a-half or even two hours longer at the weekend. "However, sleep debt cannot always be caught up in two nights and can build up over time”, explains the neurobiologist. "It is estimated that one-third of the French population suffers from chronic sleep debt.” The effects of acute sleep deprivation are well characterized, and notably include poor concentration, impaired performance, drowsiness and irritability. According to Joelle Adrien, "if someone who needs between 6h30 and 8h30 of sleep only gets 6 hours for five days straight, the repercussions on performance are the same as those of missing a whole night’s sleep.”

The long-term consequences of sleep deprivation can be far more serious, including psychiatric problems and learning difficulties. And recent studies have suggested that other consequences may include higher risks of cardiovascular disease, obesity and diabetes, inflammatory disease and even cancer.

**Ninety-minute cycles**

Why such repercussions? To understand, we first need to look at the different types of sleep, a complex pattern that varies not only from one individual to another but also with age. In all mammals including humans, this activity—or inactivity—to which we dedicate a third of our lives, is composed of different phases which are referred to as light, deep or slow-wave and rapid eye movement (REM) sleep. "These phases follow one another to constitute a cycle which on average lasts ninety minutes in adults, although this can vary between sixty and one-hundred-and-twenty minutes”, explains the sleep specialist. "In normal conditions, a night’s sleep consists of three to five successive cycles.” Once you fall asleep, the light sleep phase occurs within a few minutes. Brain activity slows down, but

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**Good sleep: the rules**

How to sleep better Tips from the Institut national du sommeil et de la vigilance (INSV, National Institute of Sleep & Vigilance):

- adopt regular sleeping habits. Go to bed and get up at the same times to help synchronize your waking/sleeping rhythm;
- expose yourself to sunlight. To work properly, your internal clock needs to be stimulated by natural light;
- do physical activity regularly but not after 8 p.m. In the evening, falling asleep is easier and the quality of sleep is better;
- avoid stimulants (tea, coffee, Vitamin C) after 3 p.m.; similarly, smoking and drinking in the evening are both associated with nighttime waking;
- keep the evening meal light and finish it at least two hours before going to bed; favor foods rich in slow carbohydrates (potatoes, rice, bread, pasta). These make for stable sleep by providing a constant energy supply throughout the night;
- keep the temperature in the bedroom around 18°C. Low body temperature is a trigger for going to sleep so it is better not to over-heat the bedroom;
- make the room completely dark at bedtime. Melatonin is secreted in the absence of light stimulation and triggers sleep.
short, it becomes longer in subsequent cycles, reaching 45 minutes by the end of the night. "With deep sleep accounting for nearly half of the early cycles, the first three or four hours of sleep are key to the body’s physical recovery," emphasizes Joëlle Adrien. "In the second half of the night, light slow-wave sleep takes over which is why it is easier to wake up during this stage. A good night’s sleep therefore depends not only on quantity (enough) but also quality, with the right proportions of light slow-wave sleep and REM sleep." "Enough" means knowing how much you need and adapting your lifestyle accordingly. Age is also a factor in this calculation, as the need
Synchronization of the internal clock

To switch from a waking state to sleep and get the most from this vital rest phase, tiredness alone is not enough. There is also the question of circadian rhythm and the internal clock. And here, we differ enormously. Body temperature, blood pressure, the production of hormones (like growth hormone), cognitive function, mood—almost all the body’s physiological functions are governed by a circadian rhythm, locked into a 24-hour cycle. And it is our internal clock that sets this rhythm. The internal clock is located in the hypothalamus, a structure deep inside the brain that consists of some 20,000 neurons. Under the influence of about fifteen "clock" genes, it beats out a rhythm of between 23 h 30 and 24 h 30, depending on the individual. This feature of the internal clock explains why everyone has their own genetically determined rhythm, or more accurately chronotype, which dictates whether you go to sleep earlier or later. To lock the cycle into the 24-hour day, exposure to light is key. "Without light stimulation, we would go to sleep either earlier or later every day. The light-dark cycle is necessary for correct synchronization of the biological clock and, in consequence, high quality sleep", explains Claude Gronfier, neurobiologist at the Institut cellule souche et cerveau (Stem Cell and Brain Research Institute) in Lyon and Vice-President of the Société francophone de chronobiologie (French-speaking Society of Chronobiology). "Daylight stimulation involves special photosensitive cells in the eye’s retina called melanopsin retinal ganglion cells which were discovered in 2002. These are connected to the suprachiasmatic nuclei in the hypothalamus (where the internal clock is located) which are in turn connected to other structures in the brain that control the body’s various functions." Light also stimulates the pineal gland, a small gland behind the hypothalamus which secretes melatonin. Melatonin production is initiated at the end of the day and this hormone contributes to the process of falling asleep. We are just beginning to understand more about this process of falling asleep. For a long time, scientists believed that passing from the waking state to sleep involved changes in electrical activity, generated at the same time in all the brain’s various structures. As if it were controlled by a single, central switch. But this picture has been changed as a result of investigations in epileptic patients being prepared for surgery. For a long time, brain activity could only be measured via electrodes placed on the outer skull. But now, electrodes can be inserted into the brains of epileptic patients in order to locate the foci of their seizures, which has given scientists access to new data. Using these electrophysiological recordings, Hélène Bastuji for sleep changes as we get older. Pre-pubescent children spend a long time in deep slow-wave sleep but the proportion drops down to 20-25% in adulthood, and then just 5-10% after the age of 80. Sleep at that age is lighter and more sensitive to environmental stimuli. As a result, sleep becomes less restorative with age as less time is spent in the deep slow-wave phase and nighttime waking is more frequent. In parallel, REM sleep takes up far more time in young childhood, accounting for some 80% of a new-born’s sleeping time. By the end of adolescence, this has dropped down to 20-25% and stays fairly constant through adulthood.
and her team at the Centre de recherche en neurosciences (Neuroscience Research Center) in Lyon have been able to study the various waves (that translate neuron activation) running through the brain between waking and sleeping. Two structures—that work synchronously in the waking state—drew their attention: the thalamus in the middle of the brain and the cerebral cortex, the brain’s outermost layer of neural tissue. “We observed that changes in brain activity associated with falling asleep, notably the switch to slow waves, happen first in the thalamus, up to twenty minutes before they occur in the cerebral cortex”, explains Hélène Bastuji. The cortex is the center of consciousness and the fact that it “falls asleep” later could account for the hallucinations and floating sensations so common when dropping off. “To get the impression of having fallen sleep, enough parts of the brain must have switched into slow-wave sleep.”

In the Biomedical Imaging Laboratory at La Pitié-Salpêtrière Hospital in Paris, Habib Benali and his colleagues focus on changes in how different parts of the brain interact in sleep, in particular during deep slow-wave sleep. They get volunteers to fall asleep in a functional Magnetic Resonance Imaging (fMRI) machine and directly measure their brain activity from when they fall asleep until they wake up. “We have been able to map interactions between different parts of the brain to investigate how information is being processed. Compared with the waking state, processing was more localized during the deep and REM phases of sleep. Interactions there are no longer global but are confined to regions that

Habib Benali: Inserm Unit 1146/CNRS – Université Pierre-et-Marie-Curie, Biomedical Imaging Laboratory (on secondment at Concordia)

M. Magnin et al. PNAS, 23 February 2010, doi: 10.1073/pnas.0909710107

M. Boly et al. PNAS, 10 April 2012, doi: 10.1073/pnas.1111133109
Research—using functional MRI in particular—has confirmed that neurons stimulated during the day get reactivated in each phase of sleep. But to different extents, suggesting that distinct—pre-

are closer together”, notes Habib Benali. The scientists interpret these exchanges between sub-structures during sleep as a sign of the organizing and integration of information gathered during the day as part of the memorization process. "All phases of sleep seem to be involved in transferring and consolidating the day’s information but we do not yet know at which level."

Although the respective roles of the different phases largely remain a mystery, it is now undeniable that sleep is indispensable to memorization and learning. "Slow-wave sleep, especially the deepest type, is particularly important for declarative memory—that of knowledge and facts that we are aware of and remember. REM sleep, on the other hand, appears crucial for procedural memory—that which records procedures and underlies the "know-how" required to accomplish tasks”, explains Joëlle Adrien. During sleep, neural circuits used during the day get reactivated "probably to reinforce assimilation”, adds the neurobiologist. In REM sleep, during which the brain is nearly as active as it is in waking, this sub-conscious repetition is accompanied by disconnection from the brain stem, which explains the muscle relaxation that characterizes REM sleep. A mechanism that ensures, like a safety rail, that movement is restricted and our nights—as well as those of our partners—are uninterrupted and calm.

Get rid of screens
Exposure to the light from screens of computers, televisions and tablets has one nagging disadvantage: it delays sleep. Why? The LEDs in these screens emit a high proportion of blue light to which melanopsin retinal ganglion cells are very sensitive. And these photoreceptor cells play a central role in synchronizing the biological clock and regulating sleep. Even brief exposure to a screen at the beginning of the night can reset the biological clock so that it can no longer ensure a person falls asleep quickly, a necessary prerequisite to restorative sleep. "Not to mention that the most intensive users of screens, like teenagers, tend to get less exposure to natural light which is by far the best way of synchronizing the biological clock”, adds Claude Gronfier. To avoid a lag, exposure to screens should be avoided in the two hours before going to bed. Studies in children and teenagers have shown that respecting this interval extends the night’s sleep by an average of an hour-and-a-half.
The hippocampus: the memory "conductor"

The importance of slow-wave sleep is now well established in consolidating declarative memories. And the hippocampus, a small cerebral structure located underneath the anterior hypothalamus, is fundamental to this process. Michaël Zugaro and his group at the Paris Centre interdisciplinaire de recherche en biologie (Interdisciplinary Center for Biology Research) have shown that stabilization of memories requires nocturnal dialog between the hippocampus and the cerebral cortex. "The role of the hippocampus in memorization was revealed in the late 1950s by a study on an epileptic in whom this structure had had to be ablated", explains the scientist. "His capacity to form new memories was profoundly compromised". His long-term memories, however, were preserved. On the basis of these observations, a hypothesis was proposed: while the hippocampus is essential for the formation of new memories, long-term memories are held in the cortex. And hence, dialog between these two parts of the brain are key when it comes to stabilizing memories. By recording activity in the hippocampus and cortex during sleep, scientists were able to establish a correlation between the activities observed in each of these structures. "During slow-wave sleep, neurons in the hippocampus spontaneously reproduce the activity they went through over the waking hours about once every two seconds. The cortex then seems to respond with specific brain waves", explains Michaël Zugaro. To investigate the link between these interactions and memory, the scientists conducted an experiment on rats that they placed in a rectangular chamber containing two identical objects. The next day, one of the objects was moved. The animals were able to identify it if they had spent 20 minutes in the chamber the day before but not if they had only been kept in there for three minutes. "Recordings made while the rats were asleep, just after exposure to the objects, showed that there was much more communication between cortex and hippocampus in animals which had spent a longer time with the objects, and they remembered their position the following day." To establish a link between this exchange and consolidation of the memory, the scientists wanted to reinforce coupling between the hippocampus and the cortex which they did by implanting three intracerebral electrodes into rats which had only spent three minutes with the objects. The next day, all these rats were easily able to identify the object that had been moved! "This experiment was the first to show that hippocampo-cortical coupling mediates memory consolidation during sleep", notes Michaël Zugaro. It also shows that the memorization process can be reinforced by electrical stimulation. Before it helps to fix memories on a long-term basis, the hippocampus has an astounding capacity for sorting information registered over the day, storing what is worth keeping and getting rid of what is not. This is what Géraldine Rauchs and her colleagues at the Neuropsychology Laboratory in Caen have shown, having also focused on this structure’s role during sleep. In an experiment conducted on humans, the scientists rapidly presented words to volunteers with an instruction either to "Remember" or "Forget". Half of the subjects were then allowed a normal night’s sleep whereas the other half were kept awake. Three days later, their memories were tested. The sleep-deprived subjects retrieved just as many of the "Remember" words as those who had slept normally, but they remembered more of the words they were supposed to have forgotten, suggesting that their brains had failed to correctly suppress information. Functional MRI examination of the volunteers' brain activity during memorization showed that the "Remember" words induced more hippocampal activity (see figure on the next page). "This part of the brain acts as a sort of "Table of Contents". During the day, during the declarative memorization process, specific populations of neurons are activated in response to the learning
command. These labeled neurons then get reactivated during sleep, the degree of reactivation being dependent on the importance of the information. This is the first step in memory consolidation.

"Connections between different parts of the brain during the day in the course of learning get reactivated during the night by the hippocampus", which therefore takes on the role of a conductor. The importance of a good night’s sleep for the consolidation of memories led to questions about possible links between insomnia and the development of degenerative disease at advanced age. By means of imaging examinations in patients with Alzheimer’s disease, Géraldine Rauchs has also established a correlation between difficulty falling asleep and abnormal build-up of beta-amyloid peptide in the prefrontal cortex in the anterior brain. This peptide occurs naturally in the brain, but its excessive accumulation is characteristic of neurodegenerative disease. Moreover, in people who complained of frequent waking during the night, the insular cortex was atrophic; this lateral part of the cerebral cortex is involved in generating certain waves during sleep as well as in the control of certain cognitive functions. The scientists’ aim now is to get a better understanding of sleep patterns in these people with a view to identifying markers to predict the likelihood of developing neurodegenerative disease.

"These findings support the idea that sleep might also have a role in cleaning the brain by getting rid of metabolic waste", suggests Géraldine Rauchs. "Addressing insomnia in an elderly subject might consequently be a way of slowing cognitive decline."

**Sleep apnea**

While a quantitatively inadequate amount of sleep compromises the process of memorization, poor quality sleep seems similarly to have adverse physiological repercussions. At the HP2 Hypoxia-Cardiovascular and Respiratory Physiopathology Laboratory in Grenoble, Jean-Louis Pépin and his colleagues are looking at sleep apnea and its repercussions on the cardiovascular and metabolic systems. Sleep apnea syndrome (SAS), which affects 5-20% of the population, is characterized by closure of the pharynx—complete (apnea) or partial (hypoapnea)—several times an hour while asleep. This causes various adverse effects in the body, including intermittent hypoxia in the tissues, short interruptions of sleep and major respiratory effort. Repeated episodes of asphyxia—of which the sleeper is usually unaware—cause snoring, morning tiredness, headache, drowsiness and irritability. "With episodes of hypoxia, blood pressure is kept high during the sleeping hours whereas it should drop in parallel to the drop in heart rate so that the cardiovascular system can relax and repair itself", emphasizes Jean-Louis Pépin. "We can therefore assume that intermittent hypoxia acts on blood pressure by activating the relevant part of the compromised, leading to build-up of toxic waste inside the brain", suggests Géraldine Rauchs.

Results of a memory experiment: the parts of the brain that are activated to a greater extent by “Remember” words than “Forget” words light up in green in both groups. In subjects who have slept well, the hippocampus (red) is activated to a greater extent by “Forget” words than “Remember” words compared with those who are sleep-deprived.
sympathetic nervous system.” The consequences of SAS-related hypoxia have been probed in the laboratory, initially in animal subjects. "We showed that mice experiencing intermittent hypoxia over eight hours a day for a few weeks underwent vascular remodeling and accelerated deposition of atheromatous plaque\(^3\), a major risk factor for myocardial infarction. Inflammation was also observed in adipose tissue, which can lead to the development of insulin resistance and cardiovascular disease." The research team then confirmed these results in humans by subjecting a group of young adults to intermittent hypoxia in a special "tent" over 14 nights in a row. At the end of the period, the volunteers who had been healthy at the beginning saw their blood pressure rise. This was accompanied by activation of the sympathetic nervous system which controls the body’s sub-conscious activities like heart rate and is also intimately involved in vascular and cardiac remodeling. As in the animals, the scientists observed inflammation of adipose tissue and production of pro-inflammatory cytokines\(^4\), both of which can exacerbate insulin resistance and in consequence lead to the development of diabetes. This work is ongoing to elucidate the mechanisms at play, notably by exposing cultured cells to variable oxygen tension. "Intermittent hypoxia due to repeated episodes of apnea induces oxidative stress\(^5\) in the tissues. This can lead to inflammation, insulin resistance, hardening of the arteries and hepatic steatopathy\(^6\)\)," explains Jean-Louis Pépin. To preserve the cardiovascular system, sufficient sleep of good quality is vital if the results of prospective studies are to be believed. In fact, sleeping less than six hours a night is a cardiovascular risk factor in its own right in the context, yet again, of sleep debt. Analysis of the Canadian Nurses’ Health Study cohort of 72,000 American nurses followed for ten years showed that women who slept five hours or less a night had a 45% higher risk of coronary artery damage\(^7\) in the long term, compared with those who slept eight hours a night. In the same cohort, the risk of type 2 diabetes in women who found it difficult to fall asleep was 39% higher. It thus seems to be becoming ever more obvious that insomnia can also cause metabolic prob-
most susceptible. According to a meta-analysis, the risk of overweight and obesity is two-fold higher in children and teenagers who do not sleep much. In order to see if the reverse is true, i.e. if improving sleep can affect eating habits, Karine Spiegel and her colleagues recently conducted an experiment in young overweight and obese subjects who sleep less than seven hours a night. They were subjected to two one-week experimental sequences in random order. In one, volunteers slept as they did normally. In the other, they slept for at least one extra hour each night. The results (in press) show that during the week of prolonged sleep, volunteers were less tempted by fatty and sweet food, and snacks. Offered an all-you-can-eat buffet at the end of the study, they showed themselves far more restrained than they had been after the week in which they had maintained their habitual pattern of sleep.

Phase shifts

Finally, research is tending to confirm that sleep is important in immunity. "This link has not been extensively studied. One of the most interesting experiments showed that sleep-deprived subjects are more likely to contract influenza after injection of the virus than people who slept normally. This has been confirmed in a meta-analysis carried out by an Italian group, covering 45 studies and a total of more than 600,000 subjects. Less than six hours of sleep a night raised the risk of type 2 diabetes by a factor of 28%. "Sleep deprivation impairs the regulation of carbohydrate metabolism. It also affects neuro-endocrine function, especially the system responsible for telling the brain about energy needs", explains Karine Spiegel from the Lyon Neuroscience Research Center, who has conducted experiments to investigate the underlying mechanisms. In one of these experiments, 12 young adults were subjected to two sessions—one with two nights lasting 4 hours and the other with two 10-hour nights—in random order. After sleep deprivation, there was an 18% drop in the blood concentration of leptin, a hormone that tells the brain about satiety; in parallel, there was a 28% rise in ghrelin, a hormone that acts in the opposite way and stimulates hunger. "These endocrine changes were associated with increased appetite, especially for sweet and fatty foodstuffs." The scientists also suspect that orexin—a neurotransmitter that stimulates both hunger and wakefulness—might be affected. "Sleep deprivation is accompanied by stimulation of orexin neurons which would be expected to induce increased dietary intake as a result of pleasure due to stimulation of the brain's dopaminergic systems involved in the reward pathway. This would explain the desire for particularly energy-rich foodstuffs." The youngest subjects were the

Sleep deprivation impairs the regulation of carbohydrate metabolism"
have been allowed to sleep normally", notes Sylvaine Artero. Working with her group at La Colombière Hospital in Montpellier, the scientist was able to extract new information from the epidemiological findings of the Trois cités (3C) study which followed elderly subjects for 15 years. Analyzing links between marked diurnal drowsiness and medication use, "it emerged that people who slept better took fewer medications to treat fungal and parasitic infections. The actual incidence of viral and bacterial infection could not be established because antibiotics and antiviral drugs are often used inappropriately, but the possibility is worth investigating", notes Sylvaine Artero. Although evidence of weakening of the immune system seems to be building up, the underlying physiological mechanisms remain unclear.

Be they physiological or psychological, diverse factors can interfere with sleep. Among these, special interest is accorded to the disruption of circadian rhythms, due to the potentially adverse consequences that this may entail. The most familiar is phase retardation which is common in teenagers and young adults whose sleeping hours get progressively delayed as their biological clock slows down. "These young people tend to go to bed very late and wake up spontaneously at the end of the morning. Obliged to get out of bed in the morning, their sleep debt builds up causing drowsiness, learning difficulties and emotional disturbance", emphasizes Claude Gronfier. Inversely, sleep phase may shift in the other direction in elderly people, who go to bed and get up very early. Working different shifts can also interfere with circadian rhythm. A number of analyses have shown that workers who alternate day and night shifts are more susceptible to disease than others due to the deregulation of their biological clocks. In a recent report on the health effects of night-shift work, the Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Anses, National Agency for Food, Work & the Environment) highlighted the adverse effects on cognitive function, mental health, diabetes, cardiovascular disease and cancer. The Centre international de recherche sur le cancer (CIRC, International Cancer Research Center) in Lyon has classified night-shift work as "probably carcinogenic". The Cecile Cohort that included women working exclusively at night revealed that their risk of breast cancer was 30% higher. *Although, broadly speaking, sleep problems are being better dealt with in general medicine, this is not so for problems affecting circadian rhythm*, says Claude Gronfier. Since inadequate exposure to natural light is the main cause of dysregulation of circadian rhythm, phototherapy remains the standard treatment. Administering exogenous melatonin could also be envisaged. However, as for many sleep-related problems, the best way of protecting yourself is to keep regular sleeping habits and get enough exposure to natural light. It is important to learn to listen to your body and find its natural rhythms. Sleep should be respected not as a waste of time but rather as a way of staying healthy.

To find out more

17th National Sleep Day 17 March 2017
www.journeedusommeil.org

Sylvaine Artero: Inserm Unit 1061/CNRS – Université Montpellier
- C. Berticat et al. Scientific Reports, 21 March 2016, doi: 10.1038/srep23574
- Anses, June 2016, Evaluation of health problems related to night-shift work
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