The Extraordinary Importance of Sleep

The Detrimental Effects of Inadequate Sleep on Health and Public Safety Drive an Explosion of Sleep Research

Susan L. Worley

In the inaugural issue of the *Journal of Clinical Sleep Medicine* (2005), a feature article[1] traced early milestones in the developing field of sleep medicine, which slowly emerged from the older field of sleep research during the 1970s and 1980s. Sleep medicine, the article noted, was closely linked with and made possible by the discovery of electrical activity in the brain. The examination of electroencephalogram (EEG) patterns that occur during sleep led to the classification of stages of sleep, which in turn created an important foundation for probing human sleep, discerning abnormalities, and discovering significant relationships between sleep and health. By 2005, scientists and clinicians had not only identified and clearly defined a large number of sleep disorders but had discovered that many of them were highly prevalent.

David F. Dinges, PhD

The pace of research and discovery has only accelerated since 2005, and the number of peer-reviewed sleep journals has more than tripled. Today, researchers are more deeply probing the cellular and subcellular effects of disrupted sleep, as well as the effects of sleep deprivation on metabolism, hormone regulation, and gene expression. Newer studies are strengthening known and suspected relationships between inadequate sleep and a wide range of disorders, including hypertension,[2] obesity and type- 2 diabetes,[3] impaired immune functioning,[4] cardiovascular disease and arrhythmias,[5,6] mood disorders,[7] neurodegeneration and dementia, [8,9] and even loneliness.[10]

Research findings continue to underscore early concerns about public safety that were first raised when major industrial disasters such as the Exxon Valdez oil spill were linked to inadequate sleep.[11] Related research sponsored by major organizations, including the U.S. Department of Transportation, the U.S. Department of Defense, the National Institutes of Health, and the National Aeronautics and Space Administration (NASA), has helped to inspire national initiatives aimed at improving public safety and health. However, despite the astounding acceleration in research during the past few decades, inadequate sleep due to sleep disorders, work schedules, and chaotic lifestyles continues to threaten both health and safety.

"Pushing against the wave of accelerated growth in the field has been a shoreline of indifference," says David F. Dinges, PhD, Professor and Chief of the Division of Sleep and Chronobiology in the Department of Psychiatry at the University of Pennsylvania Perelman School of Medicine. "Modern industrial pressures to use time 24 hours a day have led to shiftwork and a world in which virtually everything—law enforcement, airports and all kinds of transportation, industrial operations, and hospitals—operates 24/7. People have come to value time so much that sleep is often regarded as an annoying interference, a wasteful state that you enter into when you do not have enough willpower to work harder and longer."

It has become increasingly clear, however, that no matter how hectic our lives may be, we can no longer afford to ignore what research is telling us about the importance of sleep for our safety and mental and physical well-being.

Impact on Attention, Cognition, and Mood

While scientists are still working to identify and clarify all of the functions of sleep,[12] decades of studies—many of which have used the method of disrupting sleep and examining the consequences—have confirmed that sleep is necessary for our healthy functioning and even survival.

"We know for sure that sleep serves multiple functions," says Dr. Dinges. "Nature tends to be very parsimonious in that it often uses a single system or biology in multiple ways to optimize the functioning of an organism. We know, for example, that sleep is critical for waking cognition—that is, for the ability to think clearly, to be vigilant and alert, and sustain attention. We also know that memories are consolidated during sleep, and that sleep serves a key role in emotional regulation."

Studies conducted by Dr. Dinges and other scientists have shown that cognitive performance and vigilant attention begin to decline fairly quickly after more than 16 hours of continuous wakefulness, and that sleep deficits from partial sleep deprivation can accumulate over time, resulting in a steady deterioration in alertness. The widely used psychomotor vigilance test (PVT), a simple neurocognitive test developed by Dr. Dinges and colleagues that assesses an individual's ability to sustain attention and respond to signals in a timely manner, has proven to be an exceptionally sensitive tool for capturing dose–response effects of sleep loss on neurobehavioral functioning.[13] The PVT also reliably detects sleep deficits caused by disrupted or fragmented sleep, and/or poorly timed sleep, which is important because a growing body of evidence suggests that the continuity and timing (or circadian alignment) of sleep may be as important as the total amount of time spent sleeping.

"We know that sleep is much more restorative of waking functions and health when it is consolidated and not fragmented," explains Dr. Dinges. "That is, when sleep goes through the appropriate physiological sequences of non-REM (rapid eye movement) and REM states at night, and occurs when human sleep is temporally programmed by our circadian clock to occur.

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Such consolidated sleep is typically of a longer duration and better sleep quality than sleep taken at other times of the day, such as that which occurs with nightshift work, jet lag, and other conditions of circadian misalignment."

Dr. Dinges and his colleagues have found that people whose daily sleep duration is inadequate, or repeatedly disrupted (e.g., by obstructive sleep apnea, restless legs syndrome, pain or stress, or shiftwork or jet lag), often are not aware of their accumulating sleep deficits or the toll that these deficits can take on their waking cognitive functions, including their performance, working memory, cognitive speed, and accuracy. Inadequate sleep also can take a toll on psychological well-being, significantly affecting our emotional and psychosocial interpretation of events and exacerbating our stress levels. Studies have indicated that changes in mood may be due in part to the effects of sleep deprivation on the processing of emotional memory—in other words, our tendency to select and remember negative memories after inadequate sleep.[14]

In one study conducted by Dr. Dinges and colleagues, participants' mood was observed after they were confronted with "high" and "low" performance demands, following varying degrees of sleep deprivation.[15]

"To our surprise, those who were sleep-deprived responded to low stressors in much the same way that people without any sleep deprivation tended to respond to high stressors," said Dr. Dinges. "In other words, we tend to become much more sensitive emotionally and socially when we are sleep-deprived. That is what I like to call the 'who was at my desk or who touched my coffee cup?' phenomenon. I think we all have experienced having an extreme reaction or a very negative emotional response to a mild stressor when we have not had enough sleep."

Aiming for the Sweet Spot

How much sleep is enough? After decades of investigation, it appears that scientists have gathered enough evidence to begin to answer that question.[16]

"When duration of sleep drops below seven hours, and especially when it starts to move toward six and half hours or less, a number of different disorders begin to increase in prevalence," says Dr. Dinges. "Most experts would agree that there is a kind of sweet spot that most people should aim for, and for the average healthy adult that zone is ideally somewhere between 7 and 7 and a half hours. That is what the consensus evaluations of more than a thousand scientific articles have yielded—the consensus of evaluations conducted by the AASM (American Academy of Sleep Medicine) and Sleep Research Society jointly."

Numerous large U.S. surveys—beginning with a 1982 survey by the American Cancer Society—have been used to estimate the number of hours that most people spend sleeping. Many surveys have identified a worrisome prevalence of "short" sleepers (people who sleep 6 hours or less) among respondents, and a general trend toward decreasing sleep duration between 1975 and 2006. More recently, however, an analysis of the American Time Use Survey (ATUS), spearheaded by Mathias Basner, MD, PhD, at the University of Pennsylvania[17], has suggested that there may be cause for optimism.

"The analysis shows that there is a slight but steady increase in sleep time that stretches back to about 2003 or 2004," says Dr. Dinges. "We think this increase, which is modest—at most a minute or two more per year—is due in part to the development of the field of sleep medicine, and public and scientific reports in the media about sleep loss contributing to accidents and catastrophes, and so forth. Ever so slowly, the message that it is important not to get sleep deprived, and to get help if you have a sleep disorder, has begun to penetrate to the public."

The analysis notes that one sign of greater interest in sleep on the part of the public has been a significant increase in Google searches containing the word "sleep" since 2004. Data from the ATUS also suggest that over time, people have been willing to trade some of their daily activities in exchange for more sleep. It is important to note, says Dr. Dinges, that self-reports of time spent sleeping are not always accurate—they can be off by a half an hour or more, usually with people tending to estimate that they slept more than they did. He also notes that there is still a fairly large population sleeping 6 hours or less.

"Although there are signs that sleep time is increasing, it is not happening at nearly the dramatic rate that most experts would like to see," says Dr. Dinges. "This is especially true for vulnerable populations. There is concern about school start times and bus times affecting the sleep of children and adolescents, and about extracurricular activities at the end of the school day sometimes leading to a delay in bed times for teenagers. All of this is an ongoing, evolving picture, with more research results coming out all the time, and with consequent changes in recommendations, to make sure that at least our most vulnerable populations are getting adequate sleep."

Interindividual Differences in Vulnerability to Sleep Loss

While it is well established that the effects of sleep loss accumulate over time, with repeated exposure to inadequate, fragmented, or disrupted sleep, the degree to which individuals demonstrate adverse effects of inadequate sleep can vary considerably.[18]

"We have learned that there are astonishingly mysterious phenotypes, or trait-like differences, in how vulnerable people are to sleep loss," says Dr. Dinges. "This is still a relatively new area of research, and it has only been in the past few years that scientists have begun to replicate early findings regarding these phenotypic differences in vulnerability to the negative neurobehavioral effects of sleep loss. The interindividual differences that have been observed so far raise some extremely provocative scientific questions. We may find that there is something in waking biology that can substitute for, or somehow reduce, the impact of sleep loss on waking functioning, but thus far there is no evidence as to what that might be."

Differences among individuals exist with regard to both the effects of sleep loss and the ability *to recover* from the effects of sleep loss. Differences in performance also have been shown to be task-dependent, suggesting that people who are vulnerable to the effects of sleep loss in one or more cognitive or neurobehavioral domains may be resistant to the effects of sleep loss in others. To better understand interindividual variability, scientists are investigating possible genetic mechanisms that may underlie complex interactions between circadian and sleep homeostatic systems—the systems that affect our drive for sleep as well as our alertness and performance during waking

Table 1 ICSD-3 Major Diagnostic Sections *	
Insomnia	Difficulty getting to sleep or staying asleep, with associated daytime consequences.
Sleep-related breathing disorders	Obstructive sleep apnea (cessation of breathing due to upper airway obstruction), central sleep apnea (cessation of breathing due to absent respiratory effort), and hypoventilation disorders (shallow breathing due to a variety of medical conditions).
Central disorders of hypersomnolence	Excessive daytime sleepiness not due to other sleep disorders. These include narcolepsy, idiopathic hypersomnolence, and insufficient sleep syndrome.
Circadian rhythm sleep–wake disorders	Abnormalities of sleep–wake cycles due to misalignment between the biological clock and customary or required sleep–wake times. These include delayed or advanced sleep phase, shift work disorder, and jet lag.
Parasomnias	Abnormal behaviors or events arising from sleep. These include sleepwalking, sleep terrors, and rapid eye-movement sleep behavior disorder.
Sleep-related movement disorders	Abnormal, usually stereotyped, recurring movements in sleep. Restless legs syndrome, although a waking sensory disorder, is included, as well as periodic limb movement in sleep and leg cramps.
Other sleep disorders	Those sleep–wake disorders not classified elsewhere, most notably environmental sleep disorder.
*Table courtesy of Michael J. Sateia, MD	

hours. A current goal is to discover biomarkers that may help predict individual performance after varying degrees of sleep loss.[19] And one hope is that biomarkers—ideally in the form of a simple "roadside" test such as a breathalyzer—may eventually be used to detect sleep loss-related impairment in drivers or in individuals responsible for operating sophisticated equipment or machinery. To date, no viable candidates have been found.

Investigators also are shedding light on the role that age may play in resilience to sleep loss. The results of one recent study indicate that younger adults are more vulnerable to the adverse effects of chronic sleep loss and recurring circadian disruption than older adults.[20] Although the neurobiological basis for these age-related differences is not yet understood, such findings may help to inform new approaches to the prevention of drowsy driving and related motor-vehicle accidents among young drivers.

Dr. Dinges emphasizes that findings regarding interindividual differences in response to sleep loss and in recovery from sleep loss should not diminish the message that adequate sleep is critical for everyone.

"Research has shown us that sleep is not an optional activity," says Dr. Dinges. "There is no question that sleep is fundamentally conserved across species and across lifespans, and that any effort to eliminate it has been unsuccessful. We must plan our lives in the time domain with a serious consideration for sleep—planning when to sleep, ensuring that we get adequate sleep, and making sure that our sleep is not disturbed by disorders or diseases, whether or not they are sleep-related."

Addressing Sleep Disorders

As connections between sleep disruption and both disease and mortality have become more firmly established, accurate and efficient diagnosis and management of sleep disorders (see Table 1) have become increasingly critical. Recent directions in the field of sleep medicine include a move toward patient-centered care, greater collaboration between specialists and primary care physicians, and the incorporation of new tools—including home-based diagnostic tests and novel electronic questionnaires—in the effort to create a comprehensive yet more personalized approach to assessment and treatment.

A chief goal is to improve the diagnosis of sleep disorders. Although approximately 70 million people in the U.S. have at least one sleep disorder, experts estimate that up to 80% of sleep disorders may go undetected or undiagnosed. One major challenge that clinicians face during the initial assessment of people with sleep disorders is the process of identifying and sorting out comorbidities. Untangling the causes and effects in bidirectional comorbidities can be particularly difficult. For example, insomnia—by far the most common sleep disorder—often is complicated by the presence of another sleep disorder, such as sleep apnea or restless legs syndrome.

"Some experts have even suggested that all cases of insomnia coexist with, or are caused by, another sleep disorder, most commonly sleep apnea," says Clete A. Kushida, MD, PhD, Professor of Psychiatry and Behavioral Sciences at Stanford, and Division Chief and Medical Director of Stanford Sleep Medicine. "I'm not sure I would go quite that far, but certainly bidirectional comorbidities among individuals who experience sleep disorders are common. For example, pain syndromes—including back pain and limb pain, especially among older patients—are common comorbidities in patients with insomnia. Mood disorders also frequently occur in patients who experience insomnia."

Comorbidities can complicate treatment and often require sleep specialists to collaborate with not only primary care physicians but also specialists in other therapeutic areas.

"If, for example, a person with insomnia also has been diagnosed with depression by a psychiatrist," says Dr. Kushida, "our goal is to work hand in hand with the psychiatrist to find the right medication. There are both sedating and alerting antidepressants, and a patient may need to try one medication for a couple of weeks to months, slowly increasing the dose to a therapeutic level, until the effect on both the depression and the patient's sleep can be determined. For some individuals, an alerting antidepressant can cause poor sleep, which in turn can exacerbate the depression. The process of achieving the right dose of the right medication can be complex, and benefits from a collaboration between specialists."

Undetected obstructive sleep apnea (OSA) in patients with chronic pain, or other serious illnesses, can result in potentially dangerous comorbidities. Opioids, for example, are known to have adverse effects on respiration, and can lead to central sleep apnea (CSA)—shallow and irregular or interrupted breathing and sustained hypoventilation—a potentially lethal condition that can intensify the consequences of OSA. These risks underscore the need to improve methods for identifying and properly diagnosing the estimated 23.5 million U.S. adults with OSA. Public education and advocacy efforts are already helping to improve detection—in part by helping to address misconceptions about OSA.

"One of the biggest misconceptions is that only people who are significantly overweight experience sleep apnea," says Dr. Kushida. "In fact, only up to 67% of people who have OSA are overweight, the rest are of normal weight. OSA also can be caused by craniofacial dysmorphism, or a defect of the airway that occurs during development. A narrow airway caused by deficient growth of the craniofacial skeleton, particularly the jaws, can become narrower and more prone to collapse with age, leading to sleep apnea."

Clete A. Kushida, MD, PhD

Treating Insomnia: The Value of Cognitive Behavioral Therapy

Insomnia, the most prevalent sleep disorder, affects approximately one third of all adults and is the most common condition that family and primary-care physicians encounter. According to the International Classification of Sleep Disorders (ICSD-3), chronic insomnia is the inability to attain sufficient sleep (despite adequate opportunity) for at least three nights per week for three months or longer, with negative daytime consequences. For most people, the disorder is transient, but for approximately 10% to 15% of those who experience insomnia (around 30 million people) it becomes chronic. Although pharmacologic treatments for insomnia (Table 2) can be effective, most experts now recommend against the long-term use of pharmacotherapy.

"If a person has been diagnosed with chronic insomnia, the only treatment that has been shown to have long-term benefit is cognitive behavioral therapy, "says Dr. Kushida. "Medications really should be considered short-term treatments, because patients tend to develop dependence on, or tolerance to, hypnotic drugs. In our clinic, we commonly see that, over time, medications stop having an effect, and that means that patients may try higher doses of a medication, or keep switching to different medications. So, medications are a temporary solution—they just put a Band-Aid on the problem of insomnia, whereas cognitive behavioral therapy targets one of the pathways toward success."

Cognitive behavioral therapy (CBT), which involves techniques that work in part by reducing cognitive and somatic arousal, is estimated to be effective in approximately 70% to 80% of people who experience chronic insomnia. Dr. Kushida notes that while drugs can sometimes be useful in the treatment of acute insomnia, they become problematic after acute insomnia transitions to chronic insomnia.

"A person might be an OK sleeper for several years, and then suddenly experience a traumatic event, such as the loss of a job, a divorce, or the death of a loved one, resulting in very poor sleep," says Dr. Kushida. "Down the road, that person might obtain a better job, overcome grief, or find a new relationship, but continue to experience insomnia. We think in some cases the transition from acute insomnia to chronic insomnia occurs because the behavioral event triggers something in the person's physiology that may lead to long-term changes. Once they are in a chronic insomnia phase, we tell patients that CBT is the only truly effective intervention."

If a patient is already taking hypnotics, Dr. Kushida says that he will gradually wean the patient off medications while introducing CBT. He notes that often it is necessary for sleep specialists to manage the expectations of chronic sufferers.

"We sometimes have to let patients with chronic insomnia know that we may never get them back to where they were when they had optimal sleep," Dr. Kushida explains. "The behavioral methods we use work well, and usually we can get patients to the point where the insomnia is having less of an impact on their quality of life. Our inability to completely restore the patient's ability to sleep well may partly be explained by as yet unidentified changes in his or her neurophysiology or neurochemistry. Some patients with chronic insomnia can begin to sleep normally again, but for the vast majority, we aim to make insomnia less of a burden on a patient's daily life."

Improving Clinical Research

In the field of sleep medicine, as in many other therapeutic areas, future directions in clinical trial research will place an emphasis on patient engagement and patient-centered outcomes.

"Perhaps the most important aim these days when developing and implementing any type of large-scale clinical research study is to incorporate the patient's perspective," says Dr. Kushida, who is currently analyzing the results of a comparative effectiveness sleep study sponsored by the Patient-Centered Outcomes Research Institute (PCORI).[22] The study, designed and conducted by a team at Stanford, introduced a new model of patient-centered, coordinated care and tested it against conventional outpatient treatment for sleep disorders.

"The patient's perspective is so invaluable in guiding the success of a study that ideally it should be incorporated right at the inception of a research question or idea," says Dr. Kushida. "When you are designing an especially complicated trial, for example, it is easy to incorporate a lot of tests and measures without being aware of the burden these can place on the participants. It's critical to learn from patients whether they are overwhelmed by the number of tests, or whether travel time or the amount of time they need to take off from work may be impractical."

Other efforts to improve clinical research include those focused on correcting for and/or eliminating several confounding variables that tend to plague sleep research. The surprising power of the placebo effect,[23] the related disconnect between

Table 2 Selected Pharmaceutical Treatments for Insomnia[21, 27]

Agent (Generic Name)	Dosage Forms	Indications/Comments
Non-benzodiazepines		
Eszopiclone	1-mg, 2-mg, and 3-mg tablets	Primarily used for sleep-onset and maintenance insomnia; intermediate-acting; no short-term usage restriction
Zolpidem	5-mg, 10-mg tablets	Primarily used for sleep-onset insomnia; short- to intermediate-acting; primarily used for sleep-onset and maintenance insomnia; controlled-release
Zaleplon	5-mg, 10-mg capsules	Primarily used for sleep-onset insomnia; maintenance insomnia as long as a 4-hour period is available for further sleep; short-acting
Benzodiazepines		
Estazolam	1-mg, 2-mg tablets	Short- to intermediate-acting
Temazepam	7.5-mg, 15-mg, and 30-mg capsules	Short- to intermediate-acting
Triazolam	0.125-mg, 0.25-mg tablets	Short-acting
Flurazepam	15-mg, 30-mg capsules	Long-acting; risk of residual daytime drowsiness
Melatonin Receptor Agonists (Non-Scheduled)		
Ramelteon	8-mg tablet	Primarily used for sleep-onset insomnia; short-acting; no short-term usage restriction
Orexin Receptor Antagonist		
Suvorexant	5-mg, 10-mg, 15-mg, and 20-mg tablets	Indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Lowest effective dose should be used.

objective and subjective evaluations of sleep loss and recovery from sleep loss, variable adherence to treatments, and, more recently, deceptive practices among clinical trial participants, are a few examples.

The placebo effect, which refers to any outcome that may be attributable to the expectations of clinical trial participants rather than to the drug or device being tested, can be especially problematic in experimental protocols that involve self-reports of sleep quality.

"Clinical trials involving patients with disorders such as insomnia or RLS that rely solely on subjective measures, or ratings of severity based on patient report, are particularly vulnerable to the placebo effect," says Dr. Kushida. "It has been demonstrated that when these patients believe that they are receiving the study drug or device the likelihood of their experiencing a positive effect can increase significantly. There have been efforts to develop or introduce new objective endpoints in these studies, which may help with this problem."

Achieving the right balance of subjective and objective measures of sleep is an important goal in both research and clinical practice. The current gold standard for objective assessment of sleep is polysomnography (PSG), which includes electrophysiological recordings of brain activity (EEG), muscle activity (EMG), and eye movements (EOG). A valuable, non-invasive method for determining sleep continuity and sleep architecture, PSG has been an indispensable objective endpoint in clinical trials, but it is expensive and not always practical. Novel approaches to objective measurement, including actigraphy, which may be used to help minimize recall bias and complement subjective measures of sleep (e.g., sleep logs or diaries), still have drawbacks.[24]

"The problem with wearable devices right now," says Dr. Kushida, "is that they tend to overestimate sleep, sometimes by as much as an hour. They also are not yet capable of accurately detecting different stages of sleep, such as non-REM and REM sleep. Because of our proximity to Silicon Valley, our laboratory tests a lot of these new devices, and often by the time we have finished testing one prototype, new ones have emerged. The product cycles are rapid, and the companies keep incorporating newer and newer technology. So, down the road, within about five to ten years, I think these devices will likely estimate sleep and detect sleep stages with precision."

Also, objective tools are needed for addressing problems with adherence to treatment. One important current aim is to detect and correct for non-obvious factors that result in failure to adhere to treatment, whether unintended or deliberate, to ensure that trial outcomes accurately reflect the efficacy of a drug, medical device, or behavioral intervention.[25] A related problem is deliberate deception by trial participants. As part of a National Heart, Lung, and Blood Institute (NHLBI)-supported study focused on detecting and correcting for adherence problems, Dr. Kushida and colleagues began to explore the prevalence of deceptive practices among clinical trial participants.[26]

"We found that deception among clinical trial participants is pretty common and that there is quite a range of deceptive practices, "says Dr. Kushida. "They include underreported drug holidays, fabrication or withholding of medical histories, pill dumping, exaggerated symptoms, and falsification of current health status. It's important that we find a way to address these deceptive practices because both the integrity of research data and the safety of participants are at risk."

Dr. Kushida adds that newer tools, such as electronic monitoring of pill dispensing and statistical predictive adherence models, may uncover and remedy pressing problems related to adherence and deceptive practices. "It already takes about 12 years for a new drug to be approved, and about three to five years for a new device to be approved. When deceptive

practices are discovered too late, it can lead to the invalidation of research findings and further delays in approving much-needed treatments."

Enhancing clinical research in the field will require a cooperative, international effort focused on advancing knowledge about sleep, circadian rhythms, and sleep disorders worldwide. During Dr. Kushida's tenure as inaugural president of the World Sleep Society (WSS), he led an initiative to create international sleep fellowships to prepare physicians and scientists from various countries for future leadership roles in basic and/or clinical sleep research. He also oversaw the development of an International Sleep Research Network, designed to help sleep scientists and clinicians find collaborators with similar clinical/research interests. As the WSS continues to offer new services and expand its programs, it will be with an awareness of the needs of disadvantaged populations and the importance of access to appropriate treatment.

"One initiative of the WSS involves reviewing current published guidelines in various countries, to determine whether they meet international standards," says Dr. Kushida. "Many guidelines are region-specific and list only medications approved in specific countries or regions. As we review the guidelines, we endorse them with caveats; we may note that particular treatments for insomnia are recommended, and when these are not available we recommend acceptable substitutes. The goal is to ensure that specialists can use practice guidelines in whichever country they practice sleep medicine, and that patients are receiving the best possible treatment available."

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