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Sleep deprivation hormesis: The shift that doesn't kill you makes you stronger

Emergency medicine approximates a prehistoric human schedule. Our ancestors spent most of their time walking, socializing, relaxing, and conserving energy [1]. When motivated, they could sprint away from a tiger or toward a mammoth. Humans fasted for hours or days, then consumed large amounts of food when they found a beehive or large mammal. Primitive humans faced a range of discomfort in their environments. Without gas-powered furnaces, car air conditioning and safe homes, they frequently felt cold, hot, and tired. By overcoming adversity, humans used *acute* stresses to become more resilient.

Human DNA evolved to detect these signals of discomfort, resulting in environmental effects on aging. Though programmed into almost all animals, aging can be modified by epigenetic forces. Small doses of toxins signaling tough times communicate the message that the organism had better live longer, or its population will go extinct. Stresses that in a very large amount would kill an individual (starvation, hypothermia, running long distances) improve health and longevity in small doses (fasting, cold exposure, exercise). Put more simply by Frederick Nietzsche, "What does not kill me makes me stronger [2]." Scientists call this hormesis: "any process in a cell or organism that exhibits a *biphasic* response to exposure to increasing amounts of a substance or condition [3]."

Google "hormesis" + an adversary in nature, and you will see positive benefits: bitter plant toxins, extreme heat/cold, intense exercise, ethanol, hypoxia, nicotine, even ionizing radiation [4,5]. Almost every stress *that evolving humans inevitably encountered* has a favorable effect *in small doses*. But one unavoidable "toxin," encountered by most of us in the ED, is accused of being harmful in *all* cases: Sleep deprivation. Surely early humans faced sleep deprivation often and for good reason: chasing prey, evading predators or enemies, staying warm, raising babies. Those who adapted would contribute genes more successfully. Then why does the medical literature show detriment to memory, problem solving, athletic performance, emotional stability, immunity, hormone balance, and other functions?

Research has shown impressive, consistent, negative effects on performance *right after* one night of missed sleep, and disturbing effects with chronic sleep deprivation. Inflammatory markers, DNA damage, and stress hormones all become grossly maladaptive. News stories, books and experts warn of this societal threat. But what if sleep deprivation were not always bad?

Insomnia improves with sleep deprivation. Most ER docs can sleep very well anywhere, anytime. Depression also responds to acute sleep deprivation, with robust evidence that one all-nighter elevates the mood [6]. Sleep deprivation may prophylax against PTSD after a fear-inducing situation [7]. Sleep deprivation mitigates inflammation and ischemic insult in brain cells, protecting hippocampal neurons from damage [8]. Twelve hours of lost sleep appears to not just protect the hippocampus, but also induces neurogenesis that persists 15 and 30 days later [9]. Yes, sleep loss increases oxidative stress and free radical formation [10], but so do exercise, fasting, and plant polyphenols [5].

Sleep researchers allow a biased hypothesis to direct research. Most protocols test individuals immediately after deprivation, neglecting measurements after adequate *recovery* sleep. Elite athletes immediately after a competition meet criteria for ICU admission. Lactate, creatine kinase, free radicals, electrolyte abnormalities, cortisol levels and other markers appear dangerously deranged. Similarly, subjects' psychomotor vigilance and emotional liability after staying up all night suggest severe acute stress.

The mystery lies in what follows. Recovery sleep leads to "dramatic returns toward normal glutathione content and liver catalase activity … restores or accentuates antioxidants and antioxidant activities [11]." Human subjects allowed ample recovery sleep resemble subjects who did not experience sleep deprivation, trending toward better response time and less sleepiness [12]. What if this paradigm were applied to shift workers? What if people who undergo small doses of sleep deprivation respond like athletes - *stronger*? By conducting systematic and longitudinal studies on effects of sleep deprivation *and* optimization of the recovery process, new studies could elucidate the complete picture of human resilience.

Admittedly, we find solace in a hypothesis that missed sleep could benefit humans. Who doesn't enjoy the camaraderie, the pride in managing an ED at night, the delicious, rapid descent to sleep on arrival home? Studies finding positive effects of sleep deprivation are indeed rare; but to prove the existence of black swans, we only need one [13]. Certainly, if you can avoid night shifts and sleep deprivation, do so. If not, implement a change in mindset: embrace the discomfort of the night shift. Practice behaviors that mitigate the negatives. Do not eat (or eat very little) or stay sedentary on the night shift [14]. Wear glasses that block blue light wavelengths [15,16]. Seek sunlight exposure during the day [17]. Bank sleep leading up to night shifts [18], and obtain ample recovery sleep [19]. Take a chance with a new theory, and use the acute stress of low dose sleep deprivation to become stronger.

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