The following is the abstract of the article discussed in the subsequent letter:

Everson, Carol A., and Linda A. Toth. Systemic bacterial invasion induced by sleep deprivation. Am J Physiol Regulatory Integrative Comp Physiol 278: R905–R916, 2000.—Profound sleep disruption in humans is generally believed to cause health impairments. Through comparative research, specific physical effects and underlying mechanisms altered by sleep deprivation are being elucidated. Studies of sleep-deprived animals previously have shown a progressive, chronic negative energy balance and gradual deterioration of health, which culminate in fatal bloodstream infection without an infectious focus. The present study investigated the conditions antecedent to advanced morbidity in sleep-deprived rats by determining the time course and distribution of live microorganisms in body tissues that are normally sterile. The tissues cultured for microbial growth included the blood, four major organs, six regional lymph nodes, the intestine, and the skin. The principal finding was early infection of the mesenteric lymph nodes by bacteria presumably translocated from the intestine and bacterial migration to and transient infection of extraintestinal sites. Presence of pathogenic microorganisms and their toxins in tissues constitutes a septic burden and chronic antigenic challenge for the host. Bacterial translocation and pathogenic sequelae provide mechanisms by which sleep deprivation appears to adversely affect health.

Sleep Deprivation and Host Defense

To the Editor: Rats subjected to total sleep deprivation (TSD) by the disk-over-water method develop increased energy expenditure, initial increases and subsequent decreases in body temperatures, and distinctive skin lesions. They die after 2–3 wk. The mediation of these changes is unknown (7). In 1993, Everson (5) reported bacteremia in five of six preterminal TSD rats and speculated that the TSD effects noted above are mediated by impaired host defense and immune function.

Everson and Toth (6) recently reported bacteria at several anatomic sites during TSD. Their conclusion that “sleep deprivation induces a chronic infectious and antigenic state that precedes outward signs of poor health” is ambiguous in the present context. “Poor health” might legitimately refer to the cachexic state immediately preceding the death of TSD rats, or it might refer to the other TSD-induced signs described above, thereby supporting Everson’s 1993 hypothesis. The latter meaning could be inferred from Everson and Toth’s suggestions of association between increased energy use and bacterial infection.

The Everson-Toth report does not support the 1993 hypothesis; it does not relate the appearance or course of bacterial infection and TSD signs. It emphasizes the early appearance of bacteria at some sites, but the earliest assays were after 5 days of TSD; all major TSD-induced signs appear earlier. The course of bacterial infection was typically erratic; the course of the noted TSD signs is typically progressive. Everson and Toth suggested that the rapid reversal of TSD signs when sleep is permitted might result from a recovery of host defense, but it is unlikely that the complete recovery of energy expenditure from twice baseline levels in 1 day is mediated by a similarly rapid restoration of host defense.

In contrast to the above, we have produced specific evidence, not cited by Everson and Toth, that fails to support bacterial invasion as responsible for the other TSD-induced signs (3). Like Everson and Toth, we tested for bacteria in blood, cecum, and several organs and found 1) much weaker correlations (all nonsignificant) between the bacterial indicators and TSD effects than between sleep loss and TSD effects (all highly significant); 2) elimination of aerobic bacteria by antibiotics did not prevent TSD effects in 4-day-deprived TSD rats; and 3) elimination of aerobic bacteria [including the facultative anaerobes named by Everson (5) as responsible for lethal bacteremia] by antibiotics did not eliminate the late hypothermia or the progression toward death. Citation by Everson and Toth of our failure to support the 1993 hypothesis and relevant analyses of their own data would have helped clarify which TSD effects are independent of bacterial infection. Prematurely attributing these effects to impaired host defense obscures promising leads to sleep function.

Everson and Toth also argued that the presumed translocation of bacteria across the intestinal wall and invasion of other organs depended on prior immunosuppression. A balanced discussion might have also included reports of similar lymphocyte responses to mitogens and antigens in TSD and control rats (1) and decreased tumor size in TSD rats relative to yoked controls (4). Benca and Quintans (2) provide a comprehensive and balanced discussion of sleep and immune function.

REFERENCES
4. Bergmann BM, Rechtschaffen A, Gilliland MA, and Quintans J. Effect of extended sleep deprivation on tumor growth in...

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REPLY

To the Editor: Rechtschaffen and Bergmann cite studies that they contend counter our suggestion that systemic bacterial invasion and antigenic challenge are a likely cause of physiological signs induced by sleep deprivation (5). A number of issues must be considered in the interpretation of those studies and the extent to which they are germane to the present study.

A 1989 publication by Benca and colleagues (2) reported the results of in vitro proliferation and antibody tests on spleen cells collected from rats late in the experimental period. The findings showed that as compared with the responses of yoked rats, about half of the sleep-deprived rats showed reduced cellular responsiveness and half showed greater responsiveness in both assays. Thus the effects were not consistent. Moreover, bacterial translocation is not dependent on impaired lymphoproliferation, and in vitro antibody production by B cells is not necessarily reflective of sepsis.

The report of an increased rate of regression of experimentally induced subcutaneous tumors in sleep-deprived versus yoked rats (4) is an intriguing finding, but this effect is nonspecific and could be related to metabolic rather than immunologic mechanisms. The report therefore did not influence how we interpreted our findings.

Impaired host defense, accompanied by systemic infections and the many physiological and metabolic changes associated with septic states, provides a plausible explanation for signs of sleep deprivation, including hypercatabolism, a well-known consequence of infectious disease states (1). We measured numbers of live bacteria and not the many intermediary physiological responses that would link the presence of bacteria to the development of other signs. Therefore, our study was not designed to reveal correlations that might establish relationships between bacterial invasion and the progressive development of other signs associated with chronic sleep deprivation.

In a study designed to show that elimination of aerobic bacteria does not markedly alter the physiological signs associated with chronic sleep deprivation, Bergmann and colleagues (3) administered an antibiotic cocktail to rats during the baseline period and the first 4 days of sleep deprivation. Despite this prophylactic treatment, however, eight sleep-deprived or yoked rats were excluded from analysis due to positive bacterial cultures, suggesting that the antibiotic regimen was largely ineffective. Data from the remaining four bacteria-negative sleep-deprived rats, combined with similar data from rats given the antibiotic cocktail late during the course of sleep deprivation, were the basis for the reported negative correlation. An absence of positive cultures of aerobic bacteria in a subset of antibiotic-treated sleep-deprived rats does not negate the finding or the implications of positive cultures of pathogenic microorganisms in untreated or even treated sleep-deprived rats. Furthermore, the absence of positive blood or tissue cultures in septicemic patients is a well-known clinical phenomenon and does not negate the state of sepsis. Moreover, factors other than aerobic bacteria (e.g., endotoxins derived from gut contents or killed translocated bacteria) can cause similar metabolic derangements. Our data indicate impaired host defense, evidenced by the presence of live bacteria in normally sterile tissues. We hypothesize that physiological changes induced by sleep deprivation allow bacteria to leave the gut, evade antimicrobial systems, and cause transient infections and finally septicemia, which leads to the death of the animal. We thus view the presence of bacteria as a sign of a more fundamental abnormality. Clinically significant bacterial translocation and posttranslocation survival of bacteria typically does not occur in the absence of local or systemic immune impairment.

REFERENCES


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