

# Spontaneous Body Temperature Fluctuations in Neurological Patients

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Received date: 07 Jun 2016; Accepted date: 06 Jul 2016; Published date: 11 Jul 2016.

Citation: Wang B, Mustroph ML, Wang H (2016) Spontaneous Body Temperature Fluctuations in Neurological Patients. *J Neurol Neurobiol* 2(4): doi <http://dx.doi.org/10.16966/2379-7150.127>

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## Abstract

Although body temperature is one of the most tightly regulated homeostatic parameters in humans, temperature abnormalities are frequently encountered in the in-hospital patient population, particularly in those with central nervous system (CNS) pathologies. CNS injuries are a prevalent cause of death and disability in young persons and on the rise among older persons. Brain and body temperature fluctuations in patients with cerebral pathologies are as of yet poorly characterized. The objective of this paper was to review our state of knowledge about spontaneous temperature fluctuations, specifically as they pertain to neurological patients. We provide an overview of the data on spontaneous temperature fluctuations (hyperthermia and hypothermia). 'Is Hotter Better?' evaluates how ambient temperature impacts human thermoregulation and health, reviews therapeutic benefits of induced hyperthermia, and discusses adverse outcomes of spontaneous hypothermia. In 'Is Colder Cooler?', we review the link between fever and poor outcomes, the detrimental effects of spontaneous hypothermia on mortality, beneficial cerebral effects of spontaneous hypothermia after ischemic brain insult, and the clinical role of therapeutic hypothermia. We conclude that the net effects of early and spontaneous body temperature fluctuations in illness likely depend on the underlying pathological process, specific tissue vulnerabilities towards temperature-induced collateral damage, and the magnitude and duration of spontaneous temperature fluctuations. The paper calls for the community to expand our attention to investigating effects of the entire range of spontaneous body temperature fluctuations in CNS illness, because at present, the therapeutic effect of targeted temperature management in neurological patients remains uncertain.

**Keywords:** Spontaneous temperature fluctuations; Hyperthermia; Hypothermia; Dysthermia; Neurological patients

## Introduction

Endothermy represents a key evolutionary innovation that enables mammals, birds, and a mesopelagic fish (the Opah) to become high-performance predators with fine-tuned neural conductance, faster reaction rates, increased muscle power, and greater capacity for sustained aerobic activity [1,2]. Under various environmental and physiological conditions, endotherms maintain a nearly constant core body temperature (normal daily variation of 0.5°C in humans) but allow other fundamental physiological parameters (respiration, heart rate, blood pressure, etc.) to fluctuate over a much wider range [3,4]. Despite the fact that humans are endotherms, body temperature abnormalities are among the most commonly noted symptoms of in-hospital patient population [5-7]. Central nervous system (CNS) injuries are the leading cause of death and disability in persons aged 15-24 [8]. Severe and acute pathologies affecting the CNS are also becoming leading causes of overall disability and death in countries where an increasing percentage of the population is aging [9,10]. Cerebrovascular disease (stroke) alone is currently the 2<sup>nd</sup> leading cause of death globally [11]. Humans, as endotherms, regulate body temperature within a narrow range centered around a basal mean temperature that varies little in the absence of pathology. Spontaneous temperature fluctuations outside the normal range occur commonly in neurological patients and remain a significant clinical challenge with much uncertainty regarding their biological significance and optimal treatment [6,7,12-19].

Deviations of body temperature from its normal range are so common in systemic inflammation that both fever and hypothermia are symptoms included in all the recent definitions of sepsis and related syndromes

[20,21]; to date, however, research efforts in the sphere of cerebral pathology have primarily focused on spontaneous body temperature elevations and the development of interventions for hyperthermia. Despite lack of clearly demonstrated clinical benefits [16,17], standard practice and common wisdom endorse treatment of spontaneous temperature elevations in neurological patients [22]; in contrast, spontaneous temperature reductions have undeservingly received much less attention. In this paper, we analyse the current literature and review the present state of knowledge concerning spontaneous body temperature fluctuations in neurological patients with CNS illnesses. Aiming to take account of the entire range of spontaneous body temperature fluctuations in such patients, we first provide a comprehensive overview of data focusing on both ends of the spectrum (hyperthermia and hypothermia) and then discuss the data in greater detail. This paper will not discuss thermoregulation after spinal cord injury because it involves dysfunction of the peripheral cold/warm receptors, autonomic control, and sweating mechanisms that are beyond the scope of this review.

## Overview

Human thermoregulatory physiology involves systemic and complex homeostatic mechanisms. Conceptually, it consists of an afferent sensory limb with both warm-sensitive and cold-sensitive thermoreceptors, a central processing center (the hypothalamus) that controls the thermoregulatory set point, and an efferent response limb that induces appropriate heat preservation or heat loss responses. Heat in humans is generated by electron exchange in mitochondria, mostly in liver, brain, heart, and in skeletal muscle contraction. Endotherms rely on centrally released hormonal uncoupling agents to increase the rate of heat

generation. Uncoupling agents allow protons to escape from the inner mitochondrial membrane, which allows for heat generation in lieu of ATP production. Heat is preserved by peripheral vasoconstriction, muscle contraction (shivering), etc. Heat in humans is lost by convection, conduction, radiation, and evaporation; that is, by peripheral vasodilatation, sweating, etc.

The dynamics of brain-body temperature fluctuations are particularly important in patients with cerebral pathologies but have not yet been well characterized. Under normal circumstances, while brain temperature is higher than core body temperature, the two are tightly correlated [23,24]. In patients with brain injury, there may be dissociation between brain and core body temperature, such that body temperature may not be a reliable surrogate for brain temperature. This dissociation between brain and core body temperature (e.g. brain thermopooling) occurs when cerebral blood flow is insufficient to decrease brain tissue temperature. There is heterogeneity in the brain temperature based on region, a phenomenon that has been referred to as selective brain cooling [25,26]. Brain regions close to the well-ventilated scalp-sinus pathway and the anterior cranial fossa, like the frontal lobes, appear to be relatively protected from states of hyperthermia [26]. However, the majority of studies concerning spontaneous temperature alterations are based on systemic not brain temperature [27,28].

Abnormally elevated temperatures may have infectious [29-32] or non-infectious causes. Non-infectious mechanisms include conditions associated with inflammation (e.g. myocardial infarction, pancreatitis), drug hypersensitivity reactions, neurogenic fever, etc. [33-36], and hyperthermia syndromes (heat stroke, neuroleptic malignant syndrome, adrenal crisis, severe thyrotoxicosis, etc.) [27,28,37-40]. The causes of elevated body temperature fall into two categories: true fever (i.e. hypothalamic set point elevation) and hyperthermia (i.e. normal hypothalamic set point). Hypothermia can be caused by cold exposure, severe infection, endocrine abnormalities, and drug overdose [41-43]. Conceptually, it is important to distinguish between physiologically regulated or dysregulated processes leading to body temperature abnormalities. In a physiological response to acute illness, the normal hypothalamic thermoregulatory set point becomes adjusted, and the hypothalamus maintains homeostasis around this new set point. The subsequent temperature fluctuations are still physiologically regulated by the same mechanisms involved in normal temperature homeostasis. Fever is typically part of a cytokine-mediated systemic inflammatory response syndrome triggered by various infections or a range of non-infectious etiologies (trauma, major surgery, and severe pancreatitis) [30,34,35,44]. It is considered physiologically regulated due to an upward adjustment of the normal hypothalamic thermoregulatory set point [45]. Conversely, hyperthermia seen in conditions like neuroleptic malignant syndrome represents a physiological system failure to balance heat gain and loss while the hypothalamus attempts to maintain thermal homeostasis around a normal temperature set point.

There are several neurological disorders in which dysfunctional thermoregulation are a central feature despite no focal hypothalamic, brainstem, spinal lesions, or autonomic failure [46]. Paroxysmal hypothermia with hyperhidrosis (PHH), multiple sclerosis (MS), and Wernicke encephalopathy are three clinical conditions in which spontaneous episodic hypothermia may occur [46]. PHH entails episodes of hypothermia, with associated pallor, flushing, bradycardia, generalized weakness, ataxia, confusion, paroxysmal hyperthermia (reverse Shapiro syndrome), wide temperature fluctuations, and/or migraines, especially in children [46]. External warming is typically not successful [46]. While PHH is not consistently associated with any structural brain abnormalities, a central theory is that PHH is caused by a low core temperature set point as well as hyper functional sweat response due to impaired voltage-gated potassium channels that normally limit the firing

frequency of the warm-sensitive neurons in the preoptic hypothalamic area [46]. While hypothermia episodes in MS are not consistently associated with any structural brain abnormalities, in MS, as in Wernicke encephalopathy, the periaqueductal gray area (PAG), held to be a relay station for cold-response pathways, has been compromised at the same time as hypothermic episodes have been observed clinically [46-48].

Temperature regulation changes in humans with age. For example, older patients do not usually have fevers of the same magnitude as younger patients in response to infection [49,50]. A variety of reasons, including immune senescence and malnutrition, have been cited for the blunted fever response observed in older patients, but it is unclear how the blunted fever response in older patients contributes to outcomes from cerebral pathology in older age [49,50].

Best clinical practice guidelines mandate that thermoregulatory failure-induced body temperature abnormalities (heat stroke, hypothermia from cold exposure, malignant hyperthermia) require prompt, acute, and intensive care to rapidly normalize body temperature. In contrast, the appropriate clinical approach towards spontaneous body temperature fluctuations from physiologically regulated responses to acute illnesses remains a matter of debate. Furthermore, in neurological patients, a clear distinction between regulated versus dysregulated temperature fluctuations is often difficult to discern, particularly because certain CNS pathologies may directly or indirectly compromise hypothalamus function. Dysregulated temperature fluctuations in the form of neurogenic fever occur particularly frequently in patients with subarachnoid hemorrhage, intraventricular bleeds, and traumatic brain injury [51]. While the mechanisms of how CNS injury leads to dysthermia are likely multifold, one favoured mechanism for how neurogenic fever occurs is *via* hypothalamus injury [51]. From a proteomic analysis of hypothalamic injury in heatstroke rats, we know that hypothalamus injury leads to hypothalamic ischemia, apoptosis, and injury as evidenced by upregulation of L-lactate dehydrogenase, blood-brain-brain disruption *via* upregulation of glial fibrillary acidic protein, oxidative stress *via* upregulation of cytosolic dehydrogenase-1, and activated inflammation *via* downregulation of stathmin 1 [52].

### Is Hotter Better?

The metabolic production and retention of heat to maintain a body temperature above the ambient temperature is energetically expensive. Nevertheless, powerful selective advantages have allowed endotherms to evolve towards a higher and higher body temperature until a balance was reached beyond which any further temperature increase would result in deleterious effects (such as decreased protein stability) out weighing its benefits. The range of body temperatures observed in modern mammals and birds is broadly similar, suggesting a common evolutionary temperature limit that has been driven as high as possible [1].

Thomas Sydenham, the father of English medicine, magisterially stated 300 years ago: 'Fever is a mighty engine which nature brings into this world for the conquest of her enemies' [53]. As a nearly ubiquitous host response to infection, fever may confer a strong survival advantage despite its metabolic cost; conversely, lower body temperatures in patients with infections are associated with an extremely high mortality rate [54]. In the context of CNS infections, a retrospective analysis of 6,396 patients with meningitis and encephalitis suggested that early fever as high as 40.0°C or above was not associated with increased hospital mortality and may be beneficial [7]. In the early part of the 20<sup>th</sup> century, therapeutic hyperthermia was developed when Nobel laureate Julius Wagner-Jauregg induced fever in patients with neurosyphilis-related progressive paralysis by injecting them with blood from patients with malaria. His work on fever therapy effectively improved the remission rates of such paralysis from 1% to 30% [55]. Subsequently, inducing a hyperthermia of 41.7°C for six

hours in a special heat chamber was shown to cure 81% of gonorrhea cases [56]. Clearly, there is a historical precedent of hyperthermia induction in the medical field in the context of infection. In the context of brain injury, the effect of hyperthermia appears to depend on the type of neurological injury; compared to patients with fever and intracerebral hemorrhage, traumatic brain injury (TBI), or aneurysmal subarachnoid hemorrhage, patients with acute ischemic stroke with fever have the highest mortality risk [57].

As an acute response to infectious illness, spontaneous hypothermia is much less common than fever but it is significantly associated with extreme severity of disease and death [42,58,59]. An association between hypothermia and detrimental clinical outcomes has been identified in trauma patients and in patients undergoing elective surgeries [60]; in fact, hypothermia has been shown to be the most important prognostic factor for poor outcome in a large series of prospective studies of trauma patients [61-63]. In patients with non-infectious cerebral pathologies, early low body temperatures (33 to 36°C) are also associated with poor outcome [64-69].

### Is Colder Cooler?

Direct recordings of cerebral temperature in the subdural space and brain parenchyma in patients with a variety of intracranial pathologies after neurological surgery show that no specific cooling mechanism other than heat uptake by arterial blood exists that protects the delicate brain from fever, such that brain temperature is consistently the highest recorded temperature compared to other body sites, in normothermia or in fever [46,70,71]. Hypothermia tends to be well-tolerated by neurons, but according to *in vitro* studies, hyperthermia (exceeding 40°C) adversely affects neurons, glia, endothelial, and epithelial cells [46,72,73]. Indeed, fever has been associated with poor functional outcome in patients after acute ischemic stroke [24,74], intracerebral hemorrhage [75], subarachnoid hemorrhage [76,77], and TBI [78,79]; furthermore, fever has been associated with increased intensive care unit (ICU) length of stay (LOS), hospital LOS, and overall mortality [6,80]. A consistent association between fever and poor outcome was also validated in a comprehensive meta-analysis in patients with brain injury [81].

Incidence of spontaneous hypothermia in brain injury appears to range from 1% [57] to 15% [64] at ICU admission. A penetrating mechanism of TBI, injury severity, and undergoing an exploratory laparotomy before admission are independent risk factors for developing hypothermia [82,83]. Old age, co-morbid conditions, and comatose state are associated with an increased incidence of spontaneous hypothermia in patients with brain injury [57].

Based on the data that fever in brain injured patients is associated with poor outcomes [81], one might expect hypothermia to carry beneficial effects. However, a retrospective review of trauma patients showed that hypothermia on surgical ICU admission is associated with decreased survival [83]. In line with this finding, an analysis of 11,033 patients with severe TBI revealed that hypothermia at hospital admission was associated with a significant increase in mortality risk [84]. In-hospital mortality rates for patients with hypothermia at admission range from 54% to 79% [57]. Trauma patients with hypothermia at hospital admission have adjusted odds ratios for mortality three times higher than patients with normothermia [83,85], and admission hypothermia is an independent risk factor for mortality in trauma patients [85,86]. In one study of body temperature in trauma patients, mortality rate reached 100% when body temperature fell below 32°C [62,83], whereas overall mortality rate in trauma patients was 39% [87]. Taken together, the data indicate that spontaneous hypothermia in trauma patients at admission is associated with increased mortality.

In the animal literature, a small number of studies indicate a therapeutic benefit of spontaneous hypothermia, which appears to preserve brain function by protecting temperature-sensitive brain areas

from injury and limiting infarct size after an ischemic event. In one study, spontaneous hypothermia in rats after asphyxia cardiac arrest was associated with decreased mortality and less injury to the temporal cortex, parietal cortex, thalamus, CA1 and CA2 neurons in the hippocampus, subiculum, and cerebellar Purkinje cells than was seen in rats subjected to a controlled normothermia intervention [88]. The neuroprotective effect of spontaneous hypothermia persisted for six weeks [88]. Spontaneous hypothermia also appears to have a protective effect after an ischemic event in the brain. In rats that sustained permanent occlusion of the middle cerebral and transient (60-minute) occlusion of the bilateral carotid arteries to induce cerebral ischemia, spontaneous hypothermia down to 32°C was associated with decreased infarction volume compared to rats in which brain temperature was artificially maintained at 37.5°C and compared to rats in which spontaneous hypothermia was prevented for 40 minutes [89]. In another study, rats with a spontaneous brain temperature decline from 36°C to 31-30°C after a transient ischemic insult to the brain showed no striatal damage and only inconsistent damage to the CA1 neurons in the hippocampus, in contrast to rats in which striatal brain temperature was maintained at 36°C [90]. Spontaneous hypothermia of the brain in response to ischemic insult affects different brain areas differently. For instance, there is evidence that the caudoputamen is extremely temperature-sensitive to temperature increases or decreases of as little as 2°C, whereas the CA1 layer of the hippocampus appears to be temperature-sensitive in a linear rather than the step-wise fashion of the caudoputamen [91]. However, these results come from a study in which body temperatures during ischemic brain insult were maintained at 35°C, 37°C, or 39°C. It is unclear whether the differential neuronal temperature vulnerabilities of brain areas like the caudoputamen and CA1 layer of the hippocampus are identical in spontaneous as opposed to induced hypothermia.

In the clinical literature, a small number of studies indicate a therapeutic benefit of spontaneous hypothermia after asphyxia cardiac arrest [88], cerebral ischemia [89], and transient ischemic insult [90]. Therapeutic hypothermia has well-established clinical roles in ischemic brain injury due to cardiac arrest [92-96] and hypoxic ischemic neonatal encephalopathy [97,98]. In order to be therapeutic after cardiac arrest, induced hypothermia need not be extreme; in fact, a multi-center, international, randomized controlled trial in thirty-six ICUs in Europe and Australia showed that mild induced hypothermia (36°C) after the cardiac event has similar outcomes on neurological function after 180 days as moderate induced hypothermia (33°C) [93]. Another trial showed that therapeutic hypothermia with a target temperature <34°C suffices for favorable neurological outcomes post-cardiac arrest [94]. However, induced hypothermia is not a panacea. While mild hypothermia after cardiac arrest is significantly associated with good neurological recovery in most patients, mild hypothermia after cardiac arrest in patients with diabetes mellitus is actually detrimental to neurological recovery and survival outcomes [99]. More recent data suggest that normothermia (36°C) yields similar outcomes as hypothermia after cardiac arrest, which suggests that it is avoidance of fever, and not hypothermia, that is neuroprotective [95].

The role of therapeutic hypothermia in acute stroke has been investigated in several studies. A meta-analysis of 101 publications and a total of 3353 animals that examined the effect of therapeutic hypothermia after ischemic stroke found that therapeutic hypothermia after ischemic stroke reduces infarct size by 44% and neurobehavioral outcomes by 46% [100]. From a study on mice that underwent global cerebral ischemia by bilateral carotid artery occlusion with or without therapeutic hypothermia, it appears that the mechanism of hypothermia that limits infarct size is mitigating the ischemia-induced increase extracellular calcium-sensing receptors and the ischemia-induced decrease in gamma-aminobutyric acid-1B receptors (GABA-1B receptors), an effect that was particularly prominent

in the temperature-sensitive hippocampus [101]. A study of 390 acute stroke patients in Copenhagen showed that patients with hypothermia at admission had less severe strokes and lower mortality rates [12]. The Nordic Cooling Stroke Study (NOCSS), the most ambitious human randomized clinical trial assessing effects of hypothermia in acute stroke to date, intended to test the effect of temperature reduction to 35°C, but was terminated because of slow recruitment [100,102]. The NIH-funded Intravascular Cooling in the Treatment of Stroke-Longer tPA window (ICTuS-L) study tested the combination of hypothermia and intravenous tPA in acute ischemic stroke and found endovascular hypothermia after stroke with intravenous thrombolysis to be preliminarily safe but raised concerns about increased incidence of pneumonia [103,104] and decreased urine output [105] from therapeutic hypothermia. Currently, there is an ongoing European multi-center, randomized phase 3 clinical trial of therapeutic hypothermia plus best medical treatment in patients with acute ischemic stroke [106,107].

In TBI, therapeutic hypothermia has no demonstrated benefits and may be harmful. A prospective multi-center randomized trial of therapeutic hypothermia in severe TBI found that prophylactic hypothermia does not improve survival rates or functional outcomes but increases rates of complications, even though fewer patients in the hypothermia group had high intracranial pressure than in the normothermia group [65,108]. Three of four meta-analyses on therapeutic hypothermia after TBI found no benefit from therapeutic hypothermia [108-112]. Another meta-analysis found that only Asian but not American population's show decreased mortality from prophylactic hypothermia [113]. The Brain Hypothermia study (BHYP0), a multi-center randomized controlled trial of severe TBI patients, found no beneficial effects of prophylactic therapeutic hypothermia on TBI; only in young patients ( $\leq 50$ ) with evacuated mass lesions did therapeutic hypothermia increase favourable outcomes [114,115]. A recent randomized controlled trial of mild therapeutic hypothermia that improved upon limitations of previous studies found no improvements in neurological outcomes or mortality from prophylactic therapeutic hypothermia for severe TBI [116]. A multi-center international trial of therapeutic hypothermia in children with severe TBI found that therapeutic hypothermia does not improve neurologic outcomes and may in fact increase mortality [108]. Another study of children with TBI in all eight PICUs in Australia and New Zealand and one PICU in Canada found no difference in outcomes at 12 months after injury from prophylactic hypothermia compared to normothermia [117]. A multi-center randomized controlled trial of prophylactic hypothermia in TBI (POLAR trial) at sites in Australia, New Zealand, and Europe is currently underway [118]. The National Acute Brain Injury Study-Hypothermia (NABIS-H) and National Acute Brain Injury Study-Hypothermia II (NABIS-II) studies evaluated whether cooling before evacuation of traumatic intracranial hematomas protects against brain reperfusion injury and whether cooling before and after craniotomy was associated with improved outcomes [119,120]. The NABIS-H I study found some improvement in outcome of patients with hematomas and severe brain injury [119]. However, the NABIS-H II study did not show utility of hypothermia as a neuroprotective intervention for TBI; in fact, the NABIS-H II study was terminated early due to futility [120]. The recent Eurotherm study of therapeutic hypothermia (to 32°C-35°C) for intracranial pressure reduction after TBI was suspended out of safety concerns. Therapeutic hypothermia for patients with intracranial pressure over 20 mm Hg after TBI did not result in superior outcomes compared to standard treatment [121].

While a recent review of studies of a total of 1219 patients undergoing neurosurgery for a variety of reasons (from craniotomies for severe TBI to cerebral aneurysm clipping to hemicraniectomy for edema after cerebral infarction) found no harmful effects from induced hypothermia (32.5°C to 35.0°C), it also found no evidence that induced hypothermia significantly

reduced neurological disability or mortality [122]. Normothermia (36.5°C to 38.0°C) appears to be just as safe as hypothermia in neurological surgery.

### Dysthermia: Is it Best Not to Be Too Hot or Too Cold?

Intuitively, most clinicians know that extreme spontaneous body temperature fluctuations, either too low or too high (dysthermia), are harmful. In a rabbit model of bacterial infections, the greatest chance of survival correlated with a mild fever compared to either normothermia or a high fever [123]. Similarly, in humans, a retrospective cohort study (n=636,051) involving more than 300 ICUs in Australia, New Zealand, and the UK demonstrated that the lowest risk of death for patients with infection in the first 24 hours occurred at a peak temperature between 39°C–39.4°C [124]. Outside of the context of infection, both spontaneous hypothermia and fever after brain injury appear to confer a greater mortality risk than normothermia upon ICU admission [57]. In the context of cerebral pathologies, a retrospective cohort study of 45,038 patients with TBI or stroke demonstrated that early temperature below 37°C and above 39°C was associated with increased mortality [7]. In a prospective study of severe TBI patients, early temperature outside of the range of 36.5°C to 38°C was associated with a higher probability of death and poorer neurological outcome at 3-month follow-up [19].

### Conclusions

Body temperature is one of the most tightly regulated homeostatic parameters in humans, but temperature abnormalities are frequently encountered in neurologically ill patients [6]. The net effects of early and spontaneous body temperature fluctuations associated with neurological illness likely depend on the underlying pathological process (e.g. infectious versus noninfectious), the physiology condition of patients (e.g. young TBI versus elderly stroke patients), the specific tissue vulnerabilities towards collateral injuries induced by temperature changes (e.g. CNS versus other organ systems), and magnitude and duration of temperature fluctuations.

It is crucial to expand our clinical attention and research efforts to investigate the biological effects of the entire range of spontaneous body temperature fluctuations associated with CNS illnesses, particularly hypothermia. The CNS is particularly sensitive to temperature changes [23,24], and early and spontaneous brain and body temperature abnormalities are commonly observed in neurological patients [6]; therefore, temperature, as an independent therapeutic target variable, measurable even in the brain by noninvasive, indirect means such as tympanic temperature [46,125,126], warrants intense clinical attention. Collectively, available data do not yet define a clear framework for understanding how temperature fluctuations impact clinical outcomes. In addition, the therapeutic efficacy of targeted temperature management remains uncertain.

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