REVIEW ARTICLE

WILEY **Evolutionary Anthropology**
ISSUES, NEWS, AND REVIEWS

Tropical heterothermy is "cool": The expression of daily torpor and hibernation in primates

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Abstract

Living nonhuman primates generally inhabit tropical forests, and torpor is regarded as a strategy employed by cold-adapted organisms. Yet, some primates employ daily torpor or hibernation (heterothermy) under obligatory, temporary, or emergency circumstances. Though heterothermy is present in most mammalian lineages, there are only three extant heterothermic primate lineages: bushbabies from Africa, lorises from Asia, and dwarf and mouse lemurs from Madagascar. Here, we analyze their phenotypes in the general context of tropical mammalian heterothermy. We focus on Malagasy lemurs as they have been the most intensively studied and also show an unmatched range of flexibility in their heterothermic responses. We discuss the evidence for whether heterothermy should be considered an ancestral or derived condition in primates. This consideration is particularly intriguing given that an understanding of the underlying mechanisms for hibernation in lemurs opens the possibility for insight into genotype-phenotype interactions, including those with biomedical relevance for humans.

KEYWORDS
Cheirogaleus, ecophysiology, *Galago*, hypometabolism, *Microcebus*

1 | TROPICAL HETEROTHERMY IS UBIQUITOUS IN MAMMALS

Definitions of daily torpor and hibernation (see Glossary) have been traditionally applied to the study of small-bodied cold-adapted mammals in temperate and arctic environments. In this context, heterothermy is a beneficial strategy for animals with high metabolic demands in periods of energetic stress such as the need to keep warm in cold climates while facing food scarcity. More recently, the energetic-stress hypothesis has been extended to circumstances occurring at lower latitudes, including the tropics.[1] In this broader context, energetic stress can be brought about by (a) food scarcity accompanying predictable seasonal changes, (b) environmental unpredictability, for example, natural disasters like fire or extended droughts, or by (3) thermal challenges resulting from microhabitat variation, for example, elevation gradients or arid habitats. Recent studies have reported heterothermic species inhabiting tropical and subtropical habitats in Australia, Asia, continental Africa, and Madagascar.[1–5] But unlike more "traditional" temperate/arctic hibernators, which are exposed to long predictable cold seasonal habitats, tropical heterotherms are opportunistic and "thermolabile".[6] In some extreme instances, they can be heterothermic *despite* hot weather (Table 1).[2] Thus, it is becoming clear that

the traditional definitions of daily torpor/hibernation as applied to cold-climate hibernators may be inadequate to describe the range of physiological flexibility expressed by mammals in the tropics.[2]

A geographic survey of the distribution of low-latitude heterotherms reveals a disparity of information on the phenomenon of tropical heterothermy. For example, little is known about heterothermic species from the American tropics and more research is warranted.[7] Heterothermic mammals from tropical forests in Asia are also poorly understood, though this may simply be the result of fewer studies conducted in that region. Heterothermy was recently reported in the pygmy slow loris (*Nycticebus pygmaeus*) from Vietnam, which show episodic patterns of torpor rather than months-long hibernation, and additional observations also signal heterothermy in both the slender loris (*Loris tardigradus*) and the Javan slow loris (*Nycticebus javanicus*).[8–11] To date, only primates have been identified as possessing heterothermic lineages among Asian nonflying mammals (members of Chiroptera, the bats, will not be considered in this review).

Australia, on the other hand, harbors a large proportion of highly endemic fauna with idiosyncratic evolutionary histories giving rise to unequal representation of heterothermic species. In Australia, there are more than 10 mammalian families with heterothermic representatives, including species belonging to the three major mammalian lineages:

Glossary

Daily Torpor: controlled reduction in metabolic rates and, often, body temperature for periods lasting less than 24 hr. Individuals generally use torpor when they are lean. It does not require preparation and can be employed flexibly, depending on internal or external conditions.

Euthermy: active state, when homeothermic individuals are asleep or awake.

Heterothermy: temporary controlled suspension of homeothermy, including a sharp decrease in metabolic rate, where an individual's body temperature usually decreases with ambient temperature and may approximate that of the immediate environment, for example, daily torpor and hibernation.

Hibernaculum: place selected for animals to use during the hibernation season; it can be an underground cavity or a tree hole. It is generally "thermally-stable."

Hibernation: controlled decrease in metabolic rates and, often, body temperature for several weeks or months, generally interrupted by periodic arousals, where extensive fattening or food accumulation is common. Needs physiological preparation, cannot be entered spontaneously.

Hypometabolism: decreased metabolic rates, below the known homeothermic levels.

Hypothermy: decreased body temperature, usually not physiologically regulated, causing depression of physiological function and potentially death.

Homeothermy: controlled regulation of body temperature at relatively high levels and within narrow ranges.

Prolonged Torpor: Torpor episodes of more than 24 hr, up to a couple of days. Does not require preparation and can be employed flexibly, depending on internal or external conditions.

Sleep: a state characterized by changes in electrical activity of the brain, and generally defined by a set of behavioral criteria including reduced motor activity, decreased responsiveness to environmental stimuli, and rapid reversibility.

Prototheria (order Monotremata), Marsupialia (orders Dasyuromorphia, Notorycteromorphia, and Diprotodontia), and Placentaria (order Rodentia).[3] Australian mammals display the full range of heterothermic expression, including species like sugar gliders (*Petaurus breviceps*) which can use daily torpor opportunistically under extreme environmental conditions—such as storms—and the eastern pygmy possum (*Cercartetus nanus*) which can hibernate up to a year without access to food—the longest reported for any mammal.[3,12]

Similarly, Africa is home to several small-sized heterothermic mammals, including elephant shrews and golden moles (order Afrotheria), dormice (order Rodentia), and hedgehogs (order Eulipotyphla) that show evidence of torpor or hibernation.[4,13] The southern African hedgehog (*Atelerix frontalis*), for example, currently holds the record for the lowest body temperature (1°C) recorded for any Afrotropical mammal during torpor.[14] Of the large range of heterothermic mammals in African habitats, only one primate thus far, the southern lesser bushbaby (*Galago moholi*), has been shown to undergo daily or multiday torpor occasionally.[15] Other African primates, like vervet monkeys, can display minor seasonal changes in body temperature, though this physiological adjustment is different from torpor as temperature changes may not be actively regulated; further studies that assess metabolic rates in these monkeys would help determine their heterothermic potential.[16]

In Madagascar, the geographic home to lemurs, two nonvolant mammalian families have heterothermic members: the Cheirogaleidae (order Primates) and Tenrecidae (order Afrotheria).[17,18] Both mammalian groups are hypothesized to have dispersed from continental Africa to Madagascar through independent rafting episodes around 60–50 mya and 40–30 mya, respectively.[19,20] Tenrecs and cheirogaleids are small-bodied, nocturnal, and show great flexibility in their heterothermic profiles. Despite those similarities, however, these groups are phylogenetically very distant: whereas tenrecs are an independent lineage within the clade Afrotheria, and may have retained basal placental mammalian traits, cheirogaleids belong to a primate lineage that diverged from other taxa much more recently in evolutionary time.[19,20] Differences in the physiological tuning of hibernation and metabolic regulation may, in fact, signal variation in underlying mechanisms brought about by unique evolutionary histories, though it is increasingly thought that the capacity for heterothermy is ancestral in mammals, having been suppressed in lineages and species that are apparently nonheterothermic.[21]

TABLE 1 Ecophysiological variables of heterothermic primates

Species	BM	Tb	Tam	Tamx	T/H	Fat?	EnvC
Galago moholi	150	13.7	−1	31	T	No	Cold, food
Microcebus berthae	35	6.8	6.3	35	T	No	Water, food
Microcebus murinus	70	15.5	13.6	35	T/H	Yes	Water, food, heat (?)
Microcebus griseorufus	50	6.5	6	38	T/H	Yes	Water, food, heat (?)
Cheirogaleus medius	150	9.3	6	35	H	Yes	Water, food, heat (?)
Cheirogaleus sibreei	250	10.5	1	27	H	Yes	Cold, food
Cheirogaleus crossleyi	350	7.5	1	27	H	Yes	Cold, food

BM = body mass; EnvC = presumed environmental challenges; Fat? = observed fattening; Tam = ambient temperature minima; Tamx = ambient temperature maxima; Tb = body temperature; T/H = use of daily torpor or hibernation.

2 | THE "PRIMITIVE PROSIMIANS": EARLY CAPTIVE STUDIES DOCUMENTING IMPERFECT HOMEOTHERMY

Although today the term strepsirrhine is preferred to promisian (the latter including the tarsiers along with lemurs, lorises, and galagos), prosimian has been extensively used during the period of early laboratory experimentation. Since the 1950s, French researchers have been aware that a group of small-bodied Malagasy lemurs became lethargic during the winter season.[22–27] One of the first documentations of primate heterothermy was made by Bourlière and Petter-Rousseaux.[22] They reported that rectal temperatures in dwarf lemurs (*Cheirogaleus*) and mouse lemurs (*Microcebus*) approximated ambient temperature (e.g., minimum rectal temperature of 18.5°C compared to ambient temperature of 14°C) under captive conditions. They also noted decreases in appetite and activity in lemurs during the period of lethargy and body mass changes throughout the year.[22–24] They referred to this condition as "imperfect homeothermy." These observations, framed in the context of cheirogaleids as models for ancestral primates, suggested "imperfect homeothermy" as an ancestral character. Later work in captive cheirogaleids resulted in inconclusive findings: whereas some studies showed that mouse and dwarf lemurs displayed changes in body temperature and body mass when maintained at constant photoperiodic and temperature conditions, another study showed no cyclical variation in body mass when exposed to constant photoperiodic conditions.[27,28]

The sister lineage to lemurs—the lorises—displayed reduced metabolic rates when compared to other similarly-sized mammals, a condition described as hypometabolism. When temperature was measured in different body parts, lorises showed great thermal insulation provided by fur, a characteristic generally associated with cold-adapted mammals rather than tropical primates.[29] In describing their unusual condition, Müller[30] stated that "slow lorises are by no means heterothermic but homoiotherms with a 'careless' temperature regulation." The slow loris (*Nycticebus coucang*), and slender loris (*Loris tardigradus*), showed flexibility in temperature variation (~6°C) while individuals were exposed to various ambient temperature conditions (from 5 to 37°C), and they also showed relatively sharp temperature gradients from core to extremities.[30,31] A separate study reported that one slow loris (*Nycticebus coucang*) became hypothermic (body temperature of 29°C with ambient temperature of 12°C) and maintained low energy expenditure.[32] Low body temperature and relatively low metabolism, both of which contribute to reducing energetic requirements for heat production, were regarded as characteristic of lorises as a group.[32]

Fewer studies were conducted on related primates like the pottos and galagos in captivity, and evidence of heterothermy and/or hypometabolism in these groups has been inconclusive. For instance, *Perodicticus potto*[33] was found to have only ~45% of metabolic rates expected for its body mass and to "behave like an heterotherm" when exposed to low temperatures (rectal temperature can decrease to ~33°C at 10°C). *Galago demidovii* was found to have low metabolic rates in one study,[34] but slightly greater than expected in another.[35]

This characterization of lorises, and other prosimians, as hypometabolic has been more recently revised. It is generally now accepted that lower-than-expected metabolic rates are common to strepsirrhines (prosimians excluding tarsiers) as a whole, rather than being a unique characteristic of lorises or galagos.[36] Thus, hypometabolism should be limited to instances of reduced metabolism as a result of heterothermic expression (see Glossary).

3 | LINES ARE BLURRED: EXPRESSION OF PRIMATE HETEROTHERMY IN THE FIELD

Before the advent of portable devices to collect physiological data, heterothermy could not be reliably tested in the wild. A pioneering field study on southern lesser bushbabies (*Galago moholi*) found no evidence of torpor in free-ranging individuals,[37] but later work by Nowack et al.[38] reported that some individuals, under extreme circumstances, could express daily torpor.[15,38] For instance, young males and low-weight individuals were most likely to express heterothermy; however, when they did so, showed limited thermoregulatory capacities to rewarm from daily torpor.[38] Most female galagos, on the other hand, spend a large portion of the year reproducing, that is, pregnant or lactating, remaining active year round. Thus, torpor would not only interfere with embryonic development and/or milk production, but would also prevent them from accumulating substantial fat stores, a precondition for hibernation.[38] It is generally agreed that the use of torpor in galagos appears to be restricted to "emergency" situations.

More recently, heterothermy was documented in the pygmy slow loris (*Nycticebus pygmaeus*) kept under semi-captive conditions in Vietnam.[8] Some individuals expressed occasional torpor bouts for up to 63 hr, interspersed with periods of euthermy. Furthermore, reports that individuals from this species can seasonally gain body mass up to 50%, make them likely candidates for hibernation. However, more studies are warranted to confirm their ability to sustain weeks-long hibernation.[11] Observations of thermal adjustments consistent with torpor were also documented for wild and captive Javan slow lorises (*Nycticebus javanicus*) and slender lorises (*Loris tardigradus*). These reports are promising, but yet insufficient, to fully characterize the physiological capacities of these primates as habitual heterotherms.[8–10]

These largely anecdotal accounts of heterothermy in lorisiforms are informative regarding the possibility of ancestral heterothermy in strepsirrhines, though most of what we know about heterothermy in primates comes from lemur studies. The family Cheirogaleidae comprises five genera of small-bodied nocturnal lemurs (*Cheirogaleus*, *Microcebus*, *Mirza*, *Allocebus*, and *Phaner*), including the smallest primate on Earth, the pygmy mouse lemur, *Microcebus berthae* (30 g). The genus *Phaner*, traditionally included in this family,[39] has been recently linked to another group of nocturnal lemurs, the Lepilemurs.[40,41] This reassignment remains controversial however, and we prefer the traditional taxonomy until such time that this phylogenetic relationship can be more thoroughly studied.[19] The phylogenetic placement of *Phaner* is relevant for understanding the expression of heterothermy in lemurs because all cheirogaleids, with the exception of *Phaner*, are believed to be heterothermic to some degree, though little is known of *Mirza*, the giant mouse lemur, and *Allocebus*, the hairy-eared mouse lemur. Direct

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evidence of torpid behavior was reported for the former and indirect evidence (i.e., absence of sightings) for the latter.[17]

The first documentation of heterothermy in wild cheirogaleids was published by Ortmann et al.[42] who reported that sympatric species of mouse lemurs used torpor: the gray mouse lemur (*Microcebus murinus*), and Madame Berthe's mouse lemur (*Microcebus berthae*; published as *Microcebus myoxinus*). These species were maintained under semi-captive conditions, in outdoor enclosures nearby Kirindy, a dry decidu-ous forest in western Madagascar. Mouse lemurs became torpid late at night or early morning (resting phase) during the austral winter and underwent a two-step rewarming phase by passively heating up to 25 °C and endogenously producing heat to further reach euthermic lev-els. Preference for low, cool and shady places during the dry season allowed mouse lemurs to extend torpor bouts and, in doing so, save more energy.[42] Passive rewarming appeared to be critical for mouse lemurs and necessary to come out of torpor, as reports had shown that captive *Microcebus murinus* failed to arouse when ambient tempera-tures remained colder than 10 °C, and subsequently died (cited in Ref. 43). Measurements of oxygen consumption used as proxy for meta-bolic rates (Box 1) showed that mouse lemurs could save up to 60% of energetic demands by using torpor.[42] Thus, energetic savings in mouse lemurs can be enhanced by exposure to warm ambient temperature. Whereas small-bodied mammals in cold habitats need to produce excessive amounts of heat by active thermogenesis to achieve euthermy after torpor, mouse lemurs can passively begin the rewarm-ing process as they come out of torpor and consequently spend less energy to reach euthermic levels.[43–45]

Although mouse lemurs were one of the first primates reported to be heterothermic, there was a decade-long research hiatus between the work by Schmid and Ortmann in the late 1990s and new ecophy-siological studies reporting use of torpor or hibernation in other mouse lemur species or habitats. We now know that mouse lemurs can express the whole heterothermic range from daily torpor, prolonged torpor, and even months-long hibernation.[46] This opportunistic use of daily torpor or hibernation is consistent with studies describing mouse lemurs as ecological opportunists *par excellence*, because they inhabit areas where no other cheirogaleid species can survive.[47] They exploit a variety of foods and can have multiple litters per year depending on the habitat and individual physical condition.

For instance, mouse lemurs inhabiting humid littoral forests in southeast Madagascar, not only use daily torpor similarly to their coun-terparts inhabiting dry forests,[42] but they can also hibernate continually for up to 4 weeks.[48] Likewise, littoral forest mouse lemurs have body temperatures that can closely track ambient temperature, and they maintain long hibernation bouts as they warm up passively or arouse when needed. Similarly, the reddish-gray mouse lemur (*Microcebus gri-seorufus*) which inhabits the southern spiny forests, one of the most unpredictable and harsh habitats in Madagascar, displays daily, pro-longed torpor, and hibernation.[46] What makes a mouse lemur hiber-nate, use torpor, or remain active within the population may be a combination of factors. Heavier individuals, by virtue of having fat stores, will be more likely to hibernate than others,[46] but body mass alone is insufficient to explain the differential use of the physiological

spectrum, particularly between daily and prolonged torpor. Presumed hibernation has been reported in Goodman's mouse lemurs (*Microcebus lehilahytsara*) under semi-captive conditions[49] and one of us (MBB) has recently observed three individuals of this species hibernating inside a tree hole at Ankafobe forest, a tiny forest fragment in the high plateau of central Madagascar (Figure 1).[50] It is worth noting that *Microcebus lehilahytsara* is regarded a "high altitude" mouse lemur, occupying some of the coldest forests of Madagascar.[51] This makes them excellent can-didates for the study of hibernation.

Unlike their sympatric cousins, all dwarf lemurs (*Cheirogaleus*) hibernate for several months under a variety of climatic and ecological conditions.[17,52,53] The hibernation profiles of dwarf lemurs, as is sus-pected for other hibernators as well, depend on the insulation proper-ties of their hibernacula, as body temperatures during hibernation approximate that of the immediate environment.[52–55] While hibernat-ing inside well-insulated tree holes, the fat-tailed dwarf lemur, *Cheiroga-leus medius* (150 g), maintains fairly stable temperature and undergoes frequent arousals (i.e., short interruptions from hibernation triggered by endogenous heat production). Conversely, while hibernating in poorly insulated tree holes, dwarf lemurs' body temperature rises as the tree holes warm up during the day and decreases during the night (and early morning) following ambient temperature fluctuations.[52] As there is a continuum in the insulation properties of their tree holes, hibernating dwarf lemurs will experience more or less frequent arousals depending on the temperature of their hibernacula. If dwarf lemurs passively warm up to ~30 °C, they forgo endogenously triggered arousals and continue to hibernate despite drastic, daily temperature fluctuations (Figure 2).[52,56–58]

Interestingly, dwarf lemurs that passively warm up and cool down with ambient temperature expend comparable amounts of energy than those animals that hibernate at more stable temperature conditions, where they undergo arousals typical of "temperate" hibernators.[57] The *metabolic profiles*, however, may differ for dwarf lemurs occupying dif-ferent hibernacula types. This is due to the fact that metabolic reac-tions are enzyme-catalyzed and enzymatic activity is affected by the temperature of the substrate. As body temperature passively fluctu-ates, metabolic rates increase and decrease accordingly. The relation-ship between metabolism and temperature becomes particularly relevant in individuals hibernating under relatively warm conditions, because some cellular mechanisms that would otherwise be shut down during a hibernation bout may remain functional. Among critical physi-ological functions that can be compatible with hibernation bouts at rel-atively elevated temperature levels are immunological responses and the ability to sleep.[59,60]

Recent studies suggested that dwarf lemurs hibernating in buf-fered hibernacula and undergoing periodic arousals may be potentially subjected to sleep debt. Eastern dwarf lemurs, which hibernate in well-insulated underground locations, analogous to hibernacula in large trees in *Cheirogaleus medius*, restrict sleep-like patterns to arousal peri-ods, a condition similar to that of nonprimate temperate/arctic hiberna-tors. On the other hand, *Cheirogaleus* that skip arousals due to exposure to drastic temperature fluctuations show brain activity
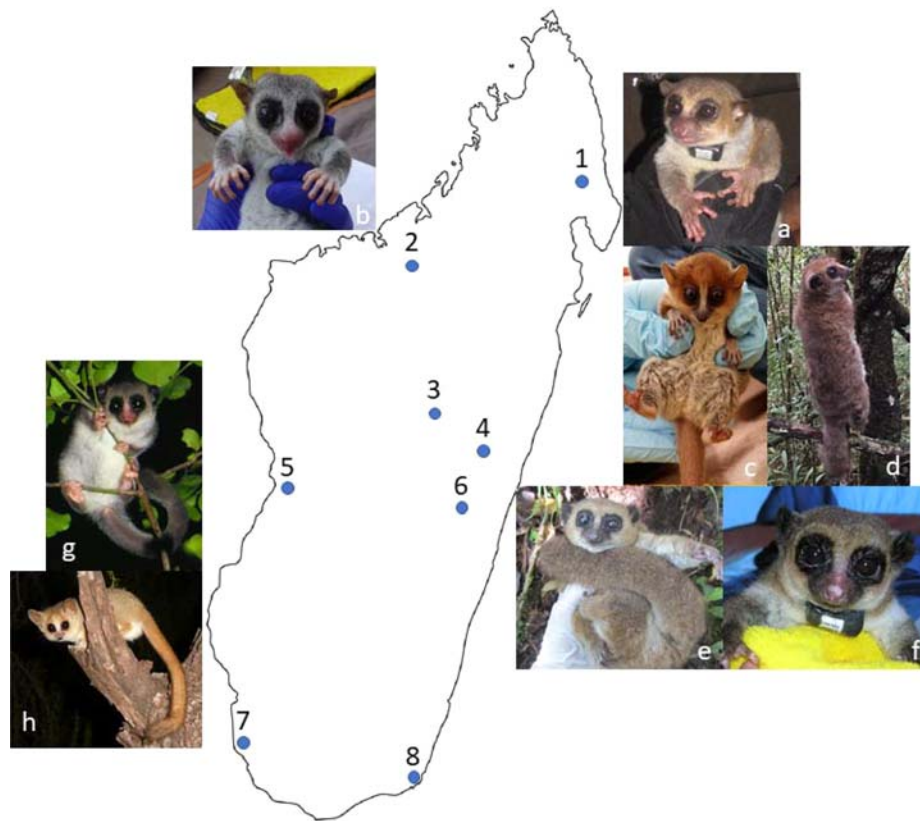
FIGURE 1 Geographic locations and photos of heterothermic lemurs mentioned in the text: 1-rainforest-Marojejy; 2-dry deciduous forest-Ankarafantsika; 3-high-altitude forest fragment-Ankafobe; 4-montane rainforest-Ambatovy; 5-dry deciduous forest-Kirindy; 6-high-altitude rainforest-Tsinjoarivo; 7-spiny forest-Tsimananpetsotsa; 8-littoral forest-Mandena; (a) *Cheirogaleus major*, (b) *Cheirogaleus medius*, (c) *Microcebus lehilahytsara*, (d) *Cheirogaleus crossleyi*, (e) *Cheirogaleus crossleyi*, (f) *Cheirogaleus sibreei*, (g) *Cheirogaleus medius*, and (h) *Microcebus griseorufus* [Color figure can be viewed at wileyonlinelibrary.com]

compatible with ("Rapid Eye Movement") REM-like sleep during the "warm" phase of the hibernation bout.[59,60]

Physiological functions related to immune responses may also be compromised during hibernation. Although it is unknown whether hibernating in warm conditions confers immunological protection to dwarf lemurs, immunological deficits to fight pathogens have been shown in several temperate hibernators.[61,62] If this is the case, immune response during hibernation bouts in high plateau dwarf lemurs may be more jeopardized than that of dwarf lemurs hibernating in warmer environments. Under these conditions, body temperature may reach high enough levels to fight pathogens during hibernation. Studies on immune function should also take into account variation in the parasite loads during hibernation, because parasite prevalence may also vary with host temperature.[63]

This is an intriguing area of research. Investigating the ability of lemurs to hibernate under warm conditions without arousing from hibernation (i.e., passive rewarming without active thermogenesis) and their capacity to withstand great temperature fluctuations during hibernation, could be insightful at multiple levels. At an ecological level, it could help assess long-term prospects of lemurs facing environmental perturbations; at a cellular level, it can help identify critical metabolic processes that can occur at temperatures different from homeothermy. In other words, if hibernation and hypothermy can be decoupled, induction of hibernation-like states may not require exposure to cold temperature, as previously thought.

4 | PHENOLOGY OF DWARF LEMUR HIBERNATION: TO HIBERNATE OR TO HIBERNATE LESS

Cheirogaleus medius hibernate for up to 7 months per year in western, dry deciduous forests, but only 5 months in the littoral forests of southeastern Madagascar (Figure 3).[64] Dry-forest dwarf lemurs that can significantly fatten during the rainy season will be in a better physiological condition to survive the food- and water-scarce period than those with poor fat storage. Lahann and Dausmann[64] hypothesized that littoral forest *Cheirogaleus medius* spend less time hibernating but more time reproducing compared to those hibernating in highly seasonal environments. Survival rates are lower in the littoral forests, however, signaling a trade-off between higher reproductive rates and shorter life spans.

Eastern dwarf lemurs, unlike their western counterparts, inhabit less seasonal rainforest environments. They are also larger than *Cheirogaleus medius* and approach the limit over which hibernation may not be energetically profitable (500 g), especially under tropical conditions.[57] A small portion of the remaining rainforests in Madagascar are comprised of high-altitude environments. Tsinjoarivo (1300 to 1700m), a forest contiguous with the central high plateau to the west and the lowlands to the east, is one the coldest habitats in Madagascar and the
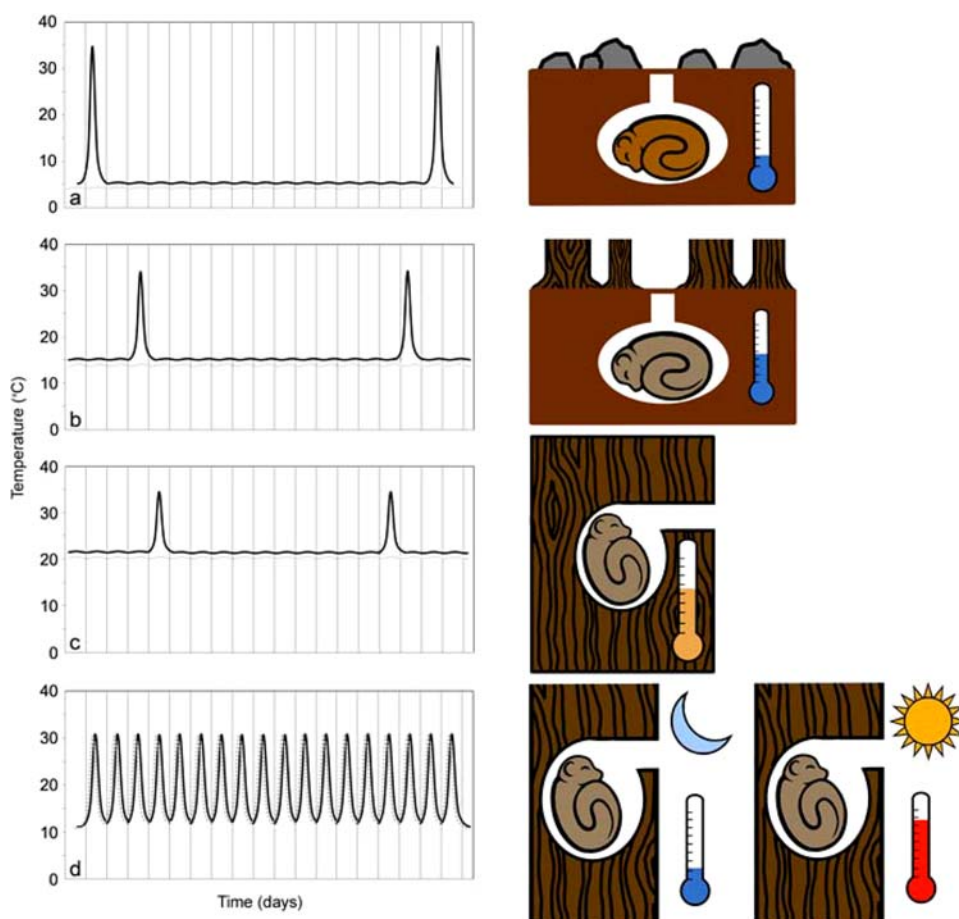
FIGURE 2 Schematic representation of hibernation profiles:(a) a cold-adapted hibernator (*Glis glis*), (b) a dwarf lemur from high-altitude rainforest (*Cheirogaleus sibreei*), a dwarf lemur from dry deciduous forest (*Cheirogaleus medius*) in (c) a highly insulated tree hole or (d) poorly insulated tree hole [Color figure can be viewed at wileyonlinelibrary.com]

home of two sympatric dwarf lemur species, *Cheirogaleus crossleyi* and *Cheirogaleus sibreei*.[54,65] *Cheirogaleus sibreei* is smaller than *Cheirogaleus crossleyi* (250 g vs. 350 g, respectively) and appears to be a high-altitude specialist. *Cheirogaleus crossleyi*, on the other hand, is found in low to high altitude forests, littoral habitats, and degraded areas.[54,66,67] During the hibernation season at Tsinjoarivo, both species hibernate

underground (Figure 4). Underground hibernation allows dwarf lemurs to maintain relatively stable temperature during heterothermy (~15°C). Maintaining stable and buffered temperatures may be critically important because ambient temperature can decrease dramatically during
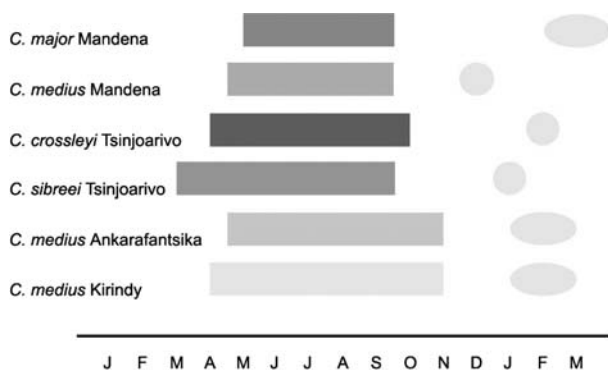
FIGURE 3 Hibernation (solid bars) and birth periods (circles, ovals) in dwarf lemurs from a littoral forest (Mandena), high altitude forest (Tsinjoarivo) and dry deciduous forests (Kirindy and Ankarafantsika)

FIGURE 4 Eastern dwarf lemur (*Cheirogaleus crossleyi*) inside natural underground hibernaculum. Top soil layer has been removed [Color figure can be viewed at wileyonlinelibrary.com]

BOX 1 Estimating field ecophysiological parameters

Due to their greater energetic demands (high mass-specific metabolic rates) and their bodies' greater surface to volume ratio (which allows for greater heat loss to the environment), small-sized species preferentially benefit from using daily torpor/hibernation. Thus, with a few exceptions, the majority of hibernating mammals are less than 1 kg.[77] Body temperature and oxygen consumption, which are often used as a proxy for metabolic rate, are the most commonly measured ecophysiological parameters in the field. These measurements are usually combined to determine the expression and degree of heterothermy and to analyze physiological adjustments of individuals to different habitats.

To collect temperature data, researchers use loggers or "temperature sensitive" transmitters, both of which have become increasingly small over the last years. They can be either implanted (subcutaneously or intraperitoneally), attached to a collar or glued onto the skin.[78] Loggers can be programed to record temperature at established intervals, and, if implanted, they require a minor surgical procedure. When using temperature sensitive transmitters, data can be readily available by measuring frequency interval lengths but must be collected "by hand" with a receiver and antenna. Data can also be recorded automatically if individuals remain in close proximity to a battery-powered set-up. An alternative is to use collars which combine a transmitter with a temperature sensor/logger to record skin temperature (T_{sk}) at predetermined intervals. These sensors inasmuch as they are in contact with skin, provide a less accurate approximation of body temperature.[79] Differences between core (T_b) and skin temperature are minimized, however, when individuals are hibernating or torpid, as they curl up in a ball pressing the transmitter close to their bodies.[79] Finally, there are also temperature-sensitive passive transponders (i.e., subcutaneously implanted microchips). By using an automatic transponder reader (within close range of individuals), subcutaneous body temperature (T_{sub}) can be measured every time an animal enters a sleeping site or repeatedly when the animal is inside the sleeping site location.[78]

Although reduction of body temperature is a good indicator of the expression of heterothermy, hypometabolism should be further confirmed by measuring rates of oxygen consumption (VO_2). This can be achieved by using a portable gas analyzer with an external pump to extract air from a resting site/container at a specified flow rate. Oxygen concentration from the individual's site is then compared to reference air (outside air), the difference translating into the uptake of oxygen by the animal in milliliters per hour (and possibly per gram body mass) (Figure 5).[57] Though using portable oxygen analyzers in the field can provide accurate estimations of metabolic rates, the animals subjected to these analyses are confined to a "metabolic chamber," which means that measurements are only reflective of resting conditions (e.g., sleeping or active resting).

To measure total energy expenditure, the doubly labeled water method is generally used. When using this method, total CO_2 is estimated from isotope traces in the water content of "labeled" individuals. Stable oxygen and hydrogen isotopes (^{18}O and ^2H) are injected at known amounts in study animals. Whereas hydrogen isotopes will disappear from "labeled" individuals as a result of water loss, oxygen isotopes will disappear as a result of water loss and respiration. Thus, oxygen isotopes will be depleted at higher rates than hydrogen isotopes. The rate of oxygen loss can then be used to assess CO_2 production. For this method to work, individuals need to be captured twice to compare the isotope ratios at known intervals. Additional information about diet and other behavioral attributes are also important to convert CO_2 production into accurate estimates of total energy expenditure.[80]
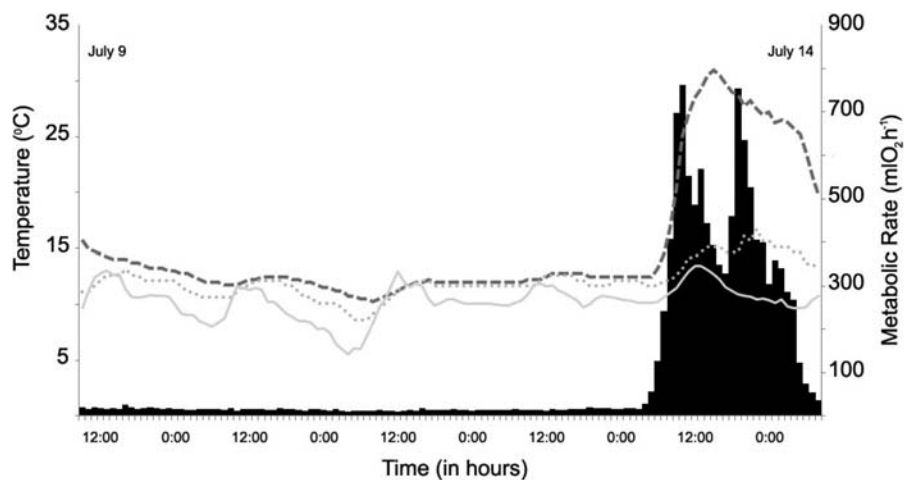
FIGURE 5 Ecophysiological profile of a hibernating eastern dwarf lemur (*Cheirogaleus crossleyi*). Broken line indicates skin temperature, dotted line temperature of hibernaculum, solid line ambient temperature and solid columns metabolic rates. Note arousal during the last 2 days as measured by an increase in skin temperature and metabolic rates

BOX 2 Energy savings in heterothermic primates

Arctic hibernators are known to save up to 99% of energy expenditure during a hibernation bout when compared to their euthermic state.[69,81–83] Tropical heterotherms, by virtue of inhabiting warmer environments, save less energy given that the differential between intrinsic and extrinsic temperatures is far less. But how much energy do they actually save? Energy savings are usually recorded as average energy expenditure during hibernation or bouts of daily torpor per species at a particular location. For instance, galagos save on average 66% during daily torpor. These estimates are derived by subtracting energy expenditure during torpor from energy expenditure during periods of euthermy. It is noteworthy that only a small number of free-ranging galagos underwent torpor and they did so during austral mid-winter only (July).[38] Energy expenditure in mouse lemurs during the dry winter season is variable due to their flexible heterothermic responses, from daily to prolonged torpor to hibernation, or remaining euthermic. However, metabolic measurements are only available for sympatric *Microcebus murinus* and *Microcebus berthae* in the dry deciduous forest, and *Microcebus griseorufus* in the spiny forest.[45,84,85] *Microcebus murinus* save between 60–80% of energy during bouts of torpor which last between 4–17 hr a day for the duration of the dry season (May–August).[42,43] Compared to mouse lemurs that remain homeothermic, individuals undergoing daily torpor can save ∼38% of daily energy expenditure (DEE).[44] *Microcebus berthae* can save 85% of energy expenditure during torpor bouts that average 10 hr but can last up to 17 hr.[84] Daily energy savings by torpid individuals reach 39%, similar to *Microcebus murinus* at the same location.[84] Daily savings by torpid *Microcebus griseorufus* amount to 21%, but torpor bouts are shorter in this species.[85]

Hibernating dwarf lemurs (*Cheirogaleus medius*) can reduce metabolic rates to more than 90% during a hibernation bout and can save about 70% of energetic requirements during the hibernation period in dry, deciduous forests. High-altitude eastern dwarf lemurs, hibernating in well-insulated (and cooler) underground burrows, can save ∼89% (*Cheirogaleus sibreei*) and 86% (*Cheirogaleus crossleyi*) of energy demands during hibernation.[55] Finally, it is worth noting that metabolic depression by daily torpor does not always result in considerable energetic savings when related to total DEE, including periods of activity. Schmid and Speakman[86] showed that DEE, as measured by the doubly labeled water technique did not differ significantly between mouse lemurs using daily torpor and those remaining euthermic. This may be due to the fact that torpid mouse lemurs remained at relatively high ambient temperature (thus, daily torpor had a negligible impact in daily energy budget) or because individuals that remain euthermic adjusted their behaviors to minimize DEE (e.g., by reducing locomotion).

the winter time, and individuals may be exposed to freezing temperatures outside their hibernacula.[54] The phenology of hibernation, that is, the timing and duration of the hibernation period, differs among and within species. *Cheirogaleus sibreei* can hibernate for 5–7 months a year, from the end of February until October, whereas the ecologically-flexible *Cheirogaleus crossleyi* hibernate between 3 and 5 months at the same location.[53,55] The shortest hibernation period lasted from early August to mid-October and was observed in an adult, lactating female that was unable to fatten until late in the season. The same individual, however, began hibernation in May the following year, demonstrating that there is inter-seasonal flexibility of individual hibernation patterns. Another sign of "physiological flexibility" in *Cheirogaleus crossleyi*, is that they can express heterothermy outside the core of the hibernation season by undergoing so-called "test drops."[54] Body temperature of dwarf lemurs occupying a nest during a test drop falls considerably during the night but never reaches values over 30°C during the hottest phase of the day in places like Tsinjoarivo. Thus, they must arouse if heterothermy lasts several days.[54]

The phenology of hibernation is similar for *Cheirogaleus crossleyi* from Ambatovy, another montane eastern rainforest (900 m altitude) north of Tsinjoarivo, albeit with milder climate conditions (Figure 1). At Ambatovy, dwarf lemurs hibernate underground between 4.5 and 6 months a year, with some individuals starting hibernation in early March and some hibernating as late as the end of September (MBB pers. obs.). Perhaps due to lower risks of freezing, some individuals can initiate hibernation inside a nest-like structure. In the course of our

field monitoring activities, we observed that two hibernating dwarf lemurs, accidentally disturbed in their nests, switched their hibernacula preferences from nests to underground locations. It is unknown if individuals hibernating inside nest-like structures could warm up passively to achieve euthermy, thus, avoiding thermogenically triggered arousals.

Virtually nothing is known about the hibernation patterns of *Cheirogaleus major*, the largest dwarf lemur species (500–600 g). At Marojejy National Park (700 m altitude) a rainforest in northern Madagascar, one individual hibernated ∼4 months, inside a thick-walled, well insulated tree hole, whereas another *Cheirogaleus major* at lower-elevation (160 m) began hibernating in a tree hole but switched to an underground location a month after hibernation started. These preliminary data show that reliance on underground hibernation is diminished in less seasonal, warmer forests. A switch to underground hibernacula may be triggered by recurrent exposure to low ambient temperature, though it is unclear whether lemurs may be responding to absolute temperature values, or the cumulative exposure to temperatures below a physiological threshold over hours or days.

Following the rationale that hibernation periods shorten as environmental conditions become less energetically challenging, it is theoretically feasible that hibernation may become dispensable in larger dwarf lemurs occupying less seasonal and warmer environments. In captivity, when *Cheirogaleus medius* are given food *ad libitum* and ambient temperature is maintained at relatively warm temperatures (∼23–25°C), lemurs reduce activity levels and feeding behavior, but tend to express daily torpor rather than hibernation.[68] If hibernation is

incompatible with reproduction, and potentially detrimental to some physiological functions, for example, increased risks of pathogen-induced infections, memory loss and high exposure to reactive oxygen species that cause cellular ageing,[69,70] why is it still prevalent in the wild, even under less seasonal conditions?

Hibernation may have selective advantages that extend beyond energy savings (Box 2). One well-known reported benefit of hibernation is avoidance of predation, which has been illustrated in several hibernating species, where hibernating individuals show higher survival rates compared to nonhibernating counterparts.[71–73] Moreover, a correlation between hibernation and longevity has been proposed for a number of hibernators, including *Cheirogaleus medius*.[68,74] More comprehensive ecophysiological studies across dwarf lemur species and habitats are needed to determine whether there is strong phylogenetic signal in the use of hibernation. Studies in captivity, additionally, could aid in understanding the genetic and molecular mechanisms involved in hibernation, for example, metabolic switches between sugar to lipid metabolism, under controlled conditions. How much of the genetic control of hibernation is mediated by environmental stimuli is the subject of increased scientific research.[75]

5 | ARE DWARF LEMURS MORE OR LESS RESILIENT TO CLIMATE CHANGE?

Heterotherms, by virtue of their capacity to reduce metabolic rates during times of energetic bottlenecks, have been regarded as resilient to climate perturbations. Torpor use has been shown to increase during environmental stress, such as fires, in non-lemur heterotherms.[3] "Daily heterotherms," including mouse lemurs, may be better equipped to cope with unpredictable environmental challenges because they are metabolically flexible and can adjust their energetic requirements on a day-to-day basis. Torpid mouse lemurs, for instance, save energy by reducing metabolic rates during the resting phase, which allows them to forage daily. Dwarf lemurs follow a more restrictive schedule, which is characteristic of long-term hibernators. Due to their need to maximize lipid storage, they depend on specialized diets, relying on resources that are only seasonally available and spatially constrained. Environmental perturbations, such as deforestation or changes in temperature/rainfall patterns, can affect the ecological "synchronicity" between active and inactive periods and disrupt the overall ecological balance between energy demands and energy availability. Moreover, hibernating lemurs (such as other hibernators not caching food) rely exclusively on lipid storage to survive the hibernation season. Unusually warmer temperatures may result in increased hibernacula temperatures, which may speed up depletion of fat reserves.

Under these circumstances, individuals may be coming out of hibernation in poor body condition at times where resources may not be yet plentiful (phenological mismatch). Temperature changes may be particularly risky in dwarf lemurs that are thermo-conforming in poorly insulated hibernacula. Risk of freezing or overheating could be lethal if hibernating lemurs are unable or unprepared to thermoregulate on demand during a physiological crisis. In sum, expression of daily torpor can be beneficial for individuals coping with unpredictable and changing environments, but commitment to long-term hibernation may render individuals more environmentally vulnerable.[76] Investigating the ecological flexibility of dwarf lemur species, the only obligate hibernators within the primates, will be critical to understand their ability to adjust to environmental perturbations, such as habitat degradation and/or climate change, and whether their reliance on hibernation put them as a disadvantage when compared to their more ecologically flexible cousins, the mouse lemurs.

6 | IS HIBERNATION ANCESTRAL OR DERIVED IN MALAGASY LEMURS?

The widespread and ubiquitous expression of heterothermy among most mammalian lineages could be explained by secondary losses or convergent gains. The intriguing hypothesis that mammals survived the K-T extinction because of their ability to escape to underground burrows and minimize energetic demands (i.e., they were heterothermic)[13] does not preclude that the use of daily torpor/hibernation could have been lost and regained multiple times throughout the mammalian phylogenetic tree. The expression of heterothermy in "basal placental mammals" such as tenrecs (which are members of the Afrotheria clade) and hedgehogs, appears to support the "ancestral heterothermy" hypothesis for mammals. It is conceivable that tenrecs retained the ancestral condition of "protoendothermy" characterized by generally low basal metabolic rates and thermolabile, ectothermic-like behaviors such as reliance of ambient temperature for passive heating after torpor bouts.[18] The great range of heterothermic expression found in tenrecs, including opportunistic daily torpor to months-long hibernation, appears to mirror, in many ways, that of the cheirogaleid primates.

Yet, whether the use of daily torpor or hibernation is considered an ancestral or derived trait within the primates is a subject of debate.[6,87,88] Similarities between tenrecs and cheirogaleids could be explained by retention of plesiomorphic traits in both groups, but also it could be explained by convergent evolution, as both small-bodied heterothermic groups were subjected to similar environmental conditions when they diversified in Madagascar, around the same time during the Miocene.[19,20] Two contrasting hypotheses are proposed to explain the expression of heterothermy in primates. One states that ancestral prosimians, that is, small-bodied primates resembling today's bushbabies, were heterothermic, a condition that lemur ancestors shared when rafting through the Indian Ocean toward Madagascar. Under this scenario, the ability to express heterothermy may have favored individuals' survival during the oceanic trip prior to arrival in Madagascar.[87,89,90] This hypothesis assumes that cheirogaleids retained heterothermy throughout their evolutionary history while the rest of lemur lineages lost, or longer use, the ability to express these metabolic strategies. A variation of this scenario suggests that ancestral colonizers were presumably not heterothermic, in the classic sense, but rather thermolabile, analogous to today's tenrecs.[87] A competing hypothesis asserts that cheirogaleids evolved heterothermy anew as a metabolic strategy to cope with major environmental challenges.[91] This scenario proposes that cheirogaleids underwent "dwarfism" during their evolution. Small bodies would have demanded higher metabolic rates,

TABLE 2 Comparison of hibernation parameters in a temperate hibernator, the edible dormouse (*Glis glis*), a high altitude eastern dwarf lemur (*Cheirogaleus sibreei*), and a dry forest dwarf lemur (*Cheirogaleus medius*)

Species	Body mass (g)	Hibernaculum temperature (°C)	Body temperature (°C)	Duration of hibernation bout (days)	Duration of hibernation season (months)	Energy savings during H (%)	Heart beats per Min	Arousal?	Duration of arousal (hr)
Glis glis	120–150	6 (2–10)	5	5–16 (up to 40)	8	98	8	Yes	24
Cheirogaleus sibreei	250–350	12 (10–15)	15[a]	3–14	5–7	89	6	Yes	12
Cheirogaleus medius	150–250	22 (10–35)	22	5–12	6–7	70	8	Yes	6
Cheirogaleus medius	150–250	10–35	10–35	Up to months	6–7	70	n/a	No	n/a

[a]Skin temperature used as proxy for body temperature.

rendering this group more vulnerable to energetic crises. Indirect support for this hypothesis comes from the fossil and paleoclimatic records. It has been suggested that ancestral primates colonizing Madagascar were large-bodied and outside the known range established for living hibernators.[88] Moreover, the divergence of the cheirogaleid clade is placed relatively late in lemur phylogeny and coincides with the establishment of current monsoon patterns, including periods characterized by cooling.[92] Scenarios accounting for both hypotheses have been recently suggested.

Perhaps a more relevant question is to address how difficult it is to turn on/off the "heterothermic switch." It appears that all mammals share the basic genetic machinery of heterothermy (Box 3) and that different species can show a variety of phenotypic responses within a physiological continuum, ranging from sporadic daily torpor to months-long hibernation depending on ecological settings. For instance, on one end of the primate spectrum, galagos can express torpor under extreme conditions in an attempt to conserve energy. This "emergency" response in galagos is not accompanied by previous fattening, but rather occurs when bodies are depleted of energy stores. On the other end of the spectrum, dwarf lemurs sustain a controlled period of suspended euthermy and reduced metabolism preceded by a period of metabolic adjustment, including efficient conversion of high sugar food resources into lipid storage. Additional behavioral changes, such as regulation of activity patterns also facilitate energetic savings.

In sum, the expression of heterothermy by ancestral lemurs cannot be confirmed; however, it is highly likely that ancestral lemurs did possess the propensity to express heterothermy in their genetic machinery, expression that, after reduction in body mass rendered this group more metabolically vulnerable, became critical in the evolution of the cheirogaleid lineage.

7 | WHAT CAN HIBERNATION STUDIES IN PRIMATES TELL US ABOUT METABOLIC DISORDERS AND DISEASE?

Dwarf lemurs, like other hibernators, exhibit physiological traits during heterothermy that would be fatal to nonhibernators. For example, heart rate is reduced to 5% of active levels, body temperature

plummets, and brain activity is virtually arrested (Table 2). How dwarf lemurs escape harmful consequences from these changes remains a mystery. Identifying the mechanisms behind the physiological extremes of hibernation in dwarf lemurs could have immense potential applications in a variety of fields. The near-future possibility to induce hibernation-like states in humans has opened a myriad of speculations stemming from science-fiction writers to scientists alike. Potential benefits to achieve "suspended animation" range from exploration of outer space, organ protection/recovery from severe injuries, and increased longevity.[5,93]

One exciting avenue for translational research is the exploration of the molecular mechanisms that prevent the expression of Alzheimer's-like symptoms despite the temporary formation of microtubular tangles during hibernation. The Alzheimer's phenotype characteristically corresponds with the formation of "neuritic plaques" comprised of hyper-phosphorilated tangles of the protein tau (associated with microtubule formation).[94] This increased phosphorylation is associated with early pathogenic states of the disease.[95] Hibernators, such as Arctic ground squirrels and Syrian hamsters, show reversible formation of highly phosphorylated and dephosphorylated states during hibernation bouts and arousals, respectively.[96] A number of aged mouse lemurs do show Alzheimer's-like symptoms, such as brain atrophy, amyloid plaques, and neurofibrillary tangles. Thus, mouse lemurs are the best available primate model to understand brain aging and disease.[95,97,98] Although relatively little work has been produced, there is indication that dwarf lemurs also show reversible phosphorylation between cycles of hibernation, which can prove highly relevant to the field of brain degenerative conditions.[99]

Another biomedical approach related to neurodegenerative diseases is examining the role of melatonin as effective protection against oxidative stress and using it as co-treatment of Parkinson's and other neurodegenerative conditions.[100] Melatonin (of pineal and extra-pineal origin) is secreted in large amounts during arousals from hibernation bouts, and is thought to contribute to reducing damage derived from ischemia reperfusion.[101] Understanding the mechanisms of how peripheral tissues withstand insufficient blood flow during hibernation might lead to better technologies for neuroprotection during cardiac surgery, stroke, or brain trauma; elucidating how hibernating animals

BOX 3 Genetic basis of hibernation

Comparative analysis of genomic data from several hibernating species can provide essential insights to specific genetic controls associated with the hibernation phenotype.[106] By measuring relative changes in gene expression levels in the hibernating physiological state versus non-hibernating physiological state, researchers can identify genes that are likely to be important for hibernation (Figure 6). Srere et al.[107] were the first to document differential gene expression to be a major player in the molecular regulation of hibernation. This study demonstrated that concentrations both of protein and mRNA expression of the molecule α2-macroglobulin increased during the hibernation season, relative to the active state, in the liver of ground squirrels (*Urocitellus richardsonii* and *Urocitellus columbianus*, published as *Spermophilus richardsonii* and *Spermophilus columbianus*). The authors postulated that the hibernation phenotype is manifest through a number of regulatory changes in genes that all mammals share, as opposed to genes that have hibernation-specific biological functions. Consequent work has highlighted the processes by which differential gene expression is involved in the switch from a summer-active state to a winter-hibernation state. With the advent of high-throughput genome-wide approaches, such as microarrays and transcriptomic sequencing (RNA-Seq), it has now become possible to investigate multiple genes and genetic pathways simultaneously. Typically, these studies explore how genes are selectively expressed during hibernation by sampling a variety of tissues (e.g., brain, white adipose tissue, brown adipose tissue, skeletal muscle, heart, and liver) at different physiological states of the hibernation cycle (i.e., active, torpor, and interbout arousals).

Large-scale transcriptomic investigations have now been conducted in some of the best-studied hibernating species, including squirrels (*Urocitellus* spp. and *Ictidomys tridecemlineatus*, previously published as *Spermophilus* spp.),[108–112] American black bears (*Ursus americanus*),[113,114] little brown bats (*Myotis lucifugus*)[115] and recently in two different species of dwarf lemurs (*Cheirogaleus medius* and *Cheirogaleus crossleyi*).[21,116] These studies reveal specific genes that might play a key role in the hibernation phenotype and similar pathways are upregulated in predictable ways in all hibernating species studied to date. Of import are genes involved in lipid and carbohydrate metabolism, blood coagulation, and circadian rhythms. Additionally, Villanueva-Cañas et al.[106] found that very few candidate genes were similar in expression responses when comparing four hibernating species (two ground squirrels, the American black bear, and the little brown bat) using comparative genomic techniques.[106] These data were presented with the caveat that genes rarely function in isolation but rather work as part of an orchestrated gene network. To that end, differentially expressed genes were then expanded to gene networks, which included genes from the same molecular pathway or that were linked by physical or genetic interactions. The authors concluded that when comparing gene networks of different hibernating species, most expanded networks comprise genes that are involved in the same biological processes. This novel approach of combing gene networks with large-scale transcriptomic data is crucial to provide a more complete picture of how differential gene expression functions to give rise to complex phenotypes, such as hibernation.
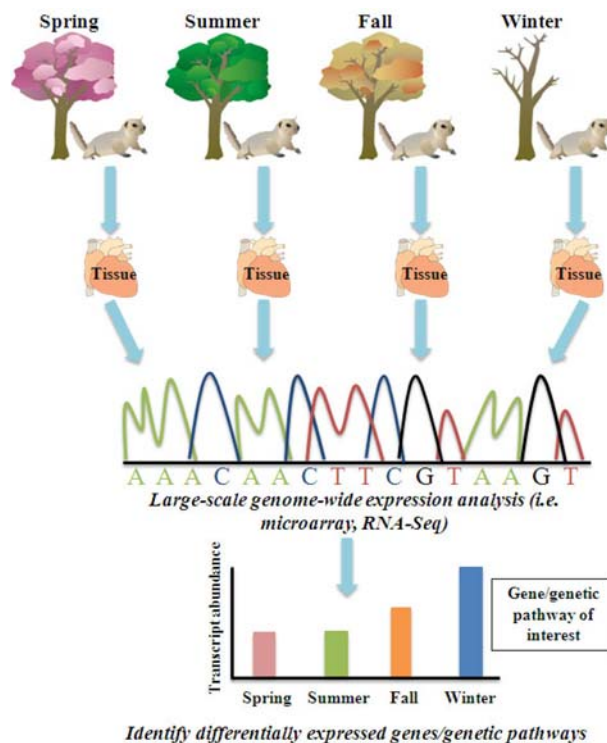
FIGURE 6 Representation of the genomic approach to the study of hibernation [Color figure can be viewed at wileyonlinelibrary.com]

avoid atrophy during 6-months of inertia might reveal opportunities relevant to immobilized or bed-ridden humans.

There is also prospective benefit to a larger portion of the human population. The possible links between hibernation and reversible insulin resistance that is generally involved in type II diabetes is a rapidly growing research area, and one that could potentially impact hundreds of thousands of diabetics.[102–104] Hibernators, particularly the dwarf lemurs, which can almost double their body mass in a couple of months, convert large amounts of high-sugar food items into lipid deposits prior to hibernation without any ill effects. In fact, they alternate between a period of insulin-resistance (corresponding to fattening) to sustain prolonged torpor, and a period when fat reserves are metabolized and depleted (lean state). Exploring the metabolic pathways that are involved in these processes can result in effective treatment of the obesity epidemic. To further augment our understanding of hibernation in relation to metabolism, insight into the gut microbiome of primate heterotherms may be revelatory. Gut consortia in non-lemur hibernators have been shown to facilitate fat deposition and weight gain during active periods in preparation for hibernation. In cold-adapted hibernators, the gut microbiome exhibits cyclical reconfigurations of community structure that correspond to active versus hibernation periods and that have implications for host metabolism. Notably, microbes preferentially digest food substrates when available, but can revert to host-derived substrates, such as mucin, when deprived of dietary foods. This reorganization of the microbial communities during fasting associated with hibernation, is critical in maintaining metabolic health and immune responses in the host.[105]

Ultimately, significant advances in these biomedical research areas will demand a compromise between applying invasive techniques on endangered primates. This conflict between the moral imperative for animal welfare and the investigation of potentially life-transforming biomedical research constitutes one of the major ethical challenges of our generation.

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