

# PHYSIOLOGY OF HIBERNATION IN BEARS

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**Abstract:** Hibernation in the Ursidae has been extensively researched over the past 30 years. This paper reviews findings of that research in the areas of general physiology and energetics; protein, fat, and bone metabolism; metabolic endocrinology; reproductive physiology and lactation; serum chemistry and hematology; and the urea:creatinine ratio. Bears in hibernation exhibit several characteristics distinct from the deep hibernation of rodents, such as a lesser reduction in body temperature, protein conservation, lack of defecation and urination, and normal bone activity. The physiological constraints of hibernation are coupled to adaptations in reproductive physiology, such as delayed implantation and lactation. I argue that urea:creatinine is not a reliable indicator of hibernation, although ongoing research is searching for an opioid-like hibernation trigger. Study of hibernation physiology will continue to bear fruit, especially in the areas of evolution, physiology, and medicine.

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Is the physiological state attained by bears during the denning period appropriately termed hibernation? Over 30 years of research in the laboratories of G.E. Folk, Jr. and R.A. Nelson, among others, have led investigators to unequivocally state that hibernation is the fitting term for the dormant or torpid state of bears during denning. Indeed, Nelson (1980) argued that bear hibernation represents the most refined response to starvation of any mammal. Bears exhibit continuous dormancy for up to 7 months without eating, drinking, defecating, or urinating. Many so-called true hibernators, such as ground squirrels (*Spermophilus* spp.), arouse every 4–10 days to feed, defecate, and urinate (Folk et al. 1976).

Watts et al. (1981) disputed definitions of hibernation based on body temperature and reaction to external stimuli, arguing that such criteria restricted the definition to small mammals. They defined mammalian hibernation as a “specialized seasonal reduction of metabolism concurrent with the environmental pressures of food inavailability and low environmental temperatures” (Watts et al. 1981:121). This definition describes hibernation by both ursids and small mammals, but would also consider many temperate ungulates hibernators, as these species also exhibit metabolic adaptations to the above-mentioned environmental pressures (Moen 1978, Loudon and Brinklow 1992, but see Mautz et al. 1992). It may be more instructive to consider that mammals exhibit a continuum of energy conservation adaptations to limited food resources, with hibernation at an end of the continuum (Moen 1978).

My discussion will review the main points of ursid hibernation physiology, focusing on black bears (*Ursus americanus*) as most work has involved this species. The

first review of this topic at the International Bear Conference was nearly 20 years ago, when Folk et al. (1976) reported that all relevant papers on bear physiology could be listed on about 1 page. A quick glance at the Literature Cited section shows that this is no longer the case.

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## GENERAL PHYSIOLOGY AND ENERGETICS

Black bears hibernate at or near normal body temperature, in contrast to the true hibernators, which hibernate with a body temperature near ambient, approaching but not falling below 0°C. Body temperatures of hibernating bears have ranged from 31.2 to 36°C (Hock 1957; Rausch 1961; Folk 1967; Folk et al. 1972, 1976; Craighead et al. 1976; Watts et al. 1981; Hellgren et al. 1990; Hissa et al. 1994). Normal body temperature is 37–38°C. Resting heart rate drops from 40 beats per minute (bpm) to as low as 8–10 bpm during hibernation (Folk 1967, Folk et al. 1972, 1976). Polar bears (*U. maritimus*) in winter that had been deprived of food exhibited bradycardia to 27 bpm (Folk et al. 1970). Brown et al. (1971) reported that cardiac output and blood pressure decreased in 2 bears from active to dormant phases, but cardiac output increased in a third bear, which from other physiological data was in an early

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arousal state. The QT segment, or relaxation interval, of electrocardiograms of bears is short, and thus more like hibernating than nonhibernating species (Folk et al. 1980).

Metabolic rates of the 3 North American bears during hibernation averaged 68, 68, and 73% of predicted basal metabolic rate (Kleiber 1975) for brown (*U. arctos*), black, and polar bears, respectively (Watts et al. 1987, Watts and Cuyler 1988, Watts and Jonkel 1988). These values are similar to those reported by Hock (1960; 50–60%) and Maxwell et al. (1988; 50%) for metabolic rates of hibernating black bears. Wide variability in metabolic rates are believed due to either natural or researcher-induced arousal (Watts and Cuyler 1988). Lowest observed metabolic rates ranged from 33% of basal metabolism in black bears to 40% in polar bears (Watts et al. 1987, Watts and Cuyler 1988). Minimal rates during hibernation in bears were twice those predicted for small hibernators, although Watts et al. (1987) argued that bear rates represented the lower limits of metabolic rate for mammals of this body mass. Reducing metabolic rate and body temperature further would require large energy expenditures for arousal and re-warming.

Weight losses in hibernating bears have ranged from 15 to 27% of predenning body weight in captive bears (Erickson and Youatt 1961, Nelson et al. 1973, Folk et al. 1976, Watts et al. 1981, Hellgren et al. 1990, Hissa et al. 1994) and 16 to 37% in wild bears (Tietje and Ruff 1980, Maxwell et al. 1988). Disturbance due to sampling may play a role in large losses of mass in hibernating individuals by increasing energy use due to arousal, increased heart rates, and activity (Watts and Cuyler 1988, Hellgren et al. 1990). Tietje and Ruff (1980) reported that loss of mass was 56% greater for bears that abandoned dens due to disturbance than for undisturbed bears. Comparatively, polar bears had the highest rates of mass loss (in percent loss/day of predenning mass) and black bears the lowest (Watts 1990).

Other physiological changes that have been observed during hibernation include possible cellular energy conservation, as sodium and potassium influx to red blood cells exhibited annual minima during hibernation (Willis et al. 1990a, 1990b). These data suggested changes in membrane transport of erythrocytes associated with hibernation, but the authors cautiously interpreted their results as either direct responses to fasting or simply seasonal changes in red cell properties. Muscle biochemistry remained relatively unchanged in black bears throughout the annual cycle, although DNA concentrations increased and the ratio of protein to DNA decreased during hibernation (Koebel et al. 1991). These changes

indicated 10–20% muscle fiber atrophy in the denning bear, which was attributed to intracellular water loss. This level of muscle atrophy was believed minimal for an extended fast and inactivity (Koebel et al. 1991).

## Protein Metabolism

The work of Ralph Nelson and colleagues has elucidated many aspects of protein metabolism in hibernation, particularly in black bears (though a “Himalayan” bear [possibly *Ursus thibetanus*] was studied by Nelson et al. [1973]). This work, though with small samples of male bears ( $n = 2-4$ ), raised many new questions. Initial study showed that there was no net formation of end-products of protein metabolism in blood or urine during hibernation (Nelson et al. 1973). Blood concentrations of amino acids, total protein, urea, and uric acid did not differ between active and hibernating states (Nelson et al. 1973). Subsequent studies reported small, significant increases in total protein concentrations and decreases in urea (Nelson et al. 1975, Ahlquist et al. 1984, Hellgren et al. 1990), contrary to expectations for an animal not eating or drinking.

Creatinine levels in captive and wild black bears have increased from 1–1.5 mg/dL during the active period to >3 mg/dL in hibernation (Brown et al. 1971; Nelson et al. 1973, 1975, 1984; Ahlquist et al. 1984; Franzmann and Schwartz 1988; Hellgren et al. 1989, 1990, 1993). This increase has not been adequately explained, though it may be related to the reduced rate of creatinine clearance associated with reduced renal plasma flow and glomerular filtration pressure during hibernation (Brown et al. 1971). The appearance of nitrogenous compounds in the urine, excepting creatinine, is greatly reduced during hibernation (Nelson et al. 1973, 1975). Fecal analysis has shown no evidence of intestinal nitrogen storage (Nelson et al. 1973).

Further study showed that the lack of accumulation of nitrogenous end-products was caused by special mechanisms unique to hibernating bears and not by starvation and lack of urea production. Bears that were denied access to food and water in the summer did not duplicate hibernation responses and became dehydrated and azotemic (Nelson et al. 1975). Urea was produced and degraded during hibernation, but at lower rates than during the active phase (Nelson et al. 1975). Total body water, blood volume, and water content of plasma and red blood cells did not change from the active to the dormant state (Brown et al. 1971, Nelson et al. 1973, 1975). Bears were considered to conserve lean body mass and use only fat combustion for energy. New evidence from polar bears (Atkinson et al. 1996), using

deuterium oxide dilution, suggested that the ability of hibernating ursids to conserve body protein is not absolute, but rather depends on the degree of fat storage at the initiation of the hibernating fast. Catabolism of body protein for energy was inversely related to the relative fatness of polar bears, a result that may explain why black bears starved in summer did not exhibit physiological responses characteristic of hibernation (black bears do not normally have large lipid stores in summer; Atkinson et al. 1996).

It has been postulated that black bears decreased protein catabolism to limit urea production as the primary means to achieve the state of hibernation (Lundberg et al. 1976). However, Lundberg et al. (1976), using radiolabeled albumin and leucine to test the above hypothesis, demonstrated that the opposite was true. The rate of protein metabolism, as measured by disappearance of labeled albumin from serum and incorporation of labeled leucine into plasma proteins, increased 3- to 5-fold during hibernation. Two reasons were postulated for the increase in protein metabolism. First, increased protein synthesis incorporated amino acids into proteins rather than allowing them to be catabolized into carbon dioxide, water, and urea. Ahlquist et al. (1984) supported this idea by showing that carbon from labeled alanine entered plasma proteins and urea in summer, but only plasma proteins in winter. Disappearance of labeled alanine was prolonged in hibernation, however. Labeled leucine was similarly incorporated into plasma proteins in hibernating bears (Nelson and Jones 1987). Second, increased protein metabolism may be necessary to meet the specific enzyme demands of the hibernating bear, such as increased production of lipolytic, gluconeogenic, proteolytic, and protein synthetic enzymes. This hypothesis has not been tested. Lundberg et al. (1976) also noted that thermogenesis may be a byproduct of increased protein turnover and could be responsible for maintaining body temperature at near normal levels.

Although incorporation of nitrogen into plasma proteins occurs faster than entry into the urea cycle and protein degradation, early researchers did not observe increases in total serum protein (Nelson et al. 1973) or albumin (Lundberg et al. 1976). However, a closer examination of these papers revealed that Nelson et al. (1973) reported an increase in total protein in serum of 0.5 mg/dL, though no significance level was reported. Lundberg et al. (1976) found albumin levels higher during hibernation in 2 of 3 bears studied, but also did not report significance levels. Subsequent reports in both captive (Ahlquist et al. 1984, Nelson and Jones 1987, Hellgren et al. 1990) and wild (Franzmann and Schwartz

1988, Hellgren et al. 1989) situations indicated that serum protein concentrations increased during hibernation to an amount similar to that predicted by Nelson et al. (1983).

The mechanisms involved with the reuse of urea nitrogen and the decrease in urea production in ursids have not been elucidated. Ahlquist et al. (1984) suggested that glycerol released during lipolysis serves as a carbon source in amino acid formation, diverting nitrogen away from urea synthesis. During hibernation, labeled carbon from glycerol appeared in alanine, serine, and plasma proteins but did not appear in urea. This increased protein turnover would also reduce urea synthesis. Nitrogen from the urea that is produced during hibernation is reused. Injection of  $^{14}\text{C}$ -labeled urea resulted in the appearance of labeled carbon in expired air (Nelson et al. 1975) and in plasma proteins and amino acids (Wolfe et al. 1982). It has been hypothesized that urea diffuses into the gut and is catabolized by bacterial urease into ammonia and carbon dioxide. These products then diffuse back to the blood, with the carbon dioxide expired and the nitrogen in ammonia recycled into amino acids (Nelson et al. 1975, Nelson 1980, Ahlquist et al. 1984). To my knowledge, gut urease activity in black bears has not been measured. Further study is necessary to follow the course of urea as it is incorporated into amino acids and proteins.

## Fat Metabolism

Fat metabolism during bear hibernation has been less studied than protein metabolism. Evidence indicates that lean body mass remains constant, at least in obese male bears (Nelson et al. 1975), while catabolism of fat supplies the energy for metabolism (Nelson et al. 1973). Fat content in 2 hibernating black bears was 36–38% (Farley and Robbins 1994) and reached 49% in a polar bear (Atkinson and Ramsay 1995) at the beginning of hibernation. The respiratory quotient (RQ—the ratio of carbon dioxide liberated to oxygen consumed), which is used to estimate the proportion of oxygen used to burn fats and carbohydrates, of hibernating bears has ranged from 0.60 to 0.73 (Hock 1957, Nelson et al. 1973, Ahlquist et al. 1984). An RQ of 0.71 represents pure fat combustion and is theoretically the lowest possible. Values <0.71 suggest that fixation of carbon dioxide is occurring.

Concentrations of blood lipids (cholesterol, phospholipids, triglycerides, free fatty acids, and ketone bodies) increase during the dormant phase (Nelson et al. 1973, Ahlquist et al. 1984, Franzmann and Schwartz 1988, Hellgren et al. 1989, 1993), apparently as a result of increased catabolism and reduced anabolism of fat.

Herminghuysen et al. (1995) reported that activity of lipoprotein lipase, an enzyme important in storage and accumulation of triglycerides in adipocytes, decreased during hibernation in black bears. However, ketosis does not occur, as in starving humans. Nelson (1980) hypothesized that fatty acid entry into metabolic pathways for ketone production is inhibited during hibernation and thus prevents ketosis. Fatty acids are thought to be converted instead to triglycerides and other lipids (Ahlquist et al. 1984). Glycerol from triglyceride metabolism is used for gluconeogenesis, in addition to its role as a carbon skeleton in amino acid formation (Ahlquist et al. 1984).

### Bone Metabolism

Floyd et al. (1990) showed that after up to 4 months of hibernation, black bears maintained bone mass and measures of bone formation at summer levels. In other species that undergo long periods of skeletal inactivity, including humans, substantial net bone loss occurs. In spring, bears exhibited hyperactive bone metabolism, which was interpreted as an adaptive response to bone remodeling during hibernation and resumption of skeletal loading after den emergence (Floyd et al. 1990). Serum calcium homeostasis during hibernation provided additional support for the idea that bone formation and resorption are in equilibrium (Floyd et al. 1990, Hellgren et al. 1990), although both increases (Hellgren et al. 1990) and decreases (Hellgren et al. 1993) in serum phosphorus have been observed from fall to hibernation. Decreases in serum activity of alkaline phosphatase during hibernation have been consistently observed (Franzmann and Schwartz 1988, Hellgren et al. 1990, 1993). Although its function is still unclear, alkaline phosphatase is essential in bone production and repair (Kuhlman 1980). Therefore, the decline in alkaline phosphatase activity in the face of normal bone formation during hibernation is intriguing.

Floyd et al. (1990) have proposed that hibernating bears produce an osteoregulatory substance that permits continued osteoblast activity in the absence of skeletal loading. Such a substance would have profound implications toward the treatment of osteoporosis.

### Metabolic Endocrinology

Studies of the activity of metabolic hormones during hibernation have provided strong endocrinological support for earlier work on protein and fat metabolism (Nelson et al. 1973, 1975, Lundberg et al. 1976). Palumbo et al. (1983) compared insulin, glucagon, and corticosteroid dynamics in active and hibernating bears. The former 2 hormones have complementary functions with

regard to metabolic function. Insulin facilitates movement of glucose into cells across cellular membranes and promotes fat deposition and protein synthesis; glucagon increases gluconeogenesis, elevates metabolic rate, and stimulates lipolysis (Dickson 1990). During hibernation, insulin concentrations were lower than during fall hyperphagia, while glucagon concentrations were highest during early hibernation (Palumbo et al. 1983). No significant differences ( $P > 0.05$ ) occurred between seasons, due to high variability and low power ( $n = 2$ ). Responses of plasma glucose, insulin, and glucagon to injections of insulin and glucagon were consistent with decreased glucose use and increased lipolysis during hibernation. Reduced renal clearance was believed responsible for the impaired disappearance of injected insulin during hibernation, prompting Palumbo et al. (1983) to speculate that this delay may promote protein conservation.

Glucocorticoid function, indexed by serum concentrations of cortisol, is increased during hibernation in both captive and field situations (Palumbo et al. 1983, Harlow et al. 1990, Hellgren et al. 1993). Harlow et al. (1990) argued that because the increase in serum cortisol was not associated with a concomitant increase in glucose or urea, the effect of higher cortisol concentrations was not gluconeogenic conversion of protein to glucose. Rather, increased cortisol levels enhanced lipid mobilization.

Thyroid function during hibernation also has been explored by Ralph Nelson and colleagues. Early reports of serum concentrations of thyroid hormones were inconclusive (Nelson et al. 1973, Lundberg et al. 1976). Examination of a thyroid gland in a bear after 2 months of hibernation revealed normal histology (Nelson et al. 1973). Lundberg et al. (1976) reported increases in total thyroxine ( $T_4$ ) but decreases in total triiodothyronine ( $T_3$ ) in all 3 bears studied. However, the authors stated that these changes "were not considered statistically significant because of the low accuracy of the assay for thyroxine and triiodothyronine at these concentrations" (Lundberg et al. 1976:720). They also reported no changes in thyroxine-binding globulin. These early results were surprising in light of the main role of the thyroid hormones, which is to increase oxygen consumption and metabolic rate. With the reduced metabolic rate characteristic of hibernation (Watts et al. 1988), thyroid function should also be reduced.

More complete study on thyroid physiology by Azizi et al. (1979), using repeated measures on 6 bears, reported declines in total and free concentrations of  $T_3$  and  $T_4$  from October through March with increasing concentrations in April and May. Probability values reported for these comparisons may be biased, because Azizi et al. (1979)

conducted paired and unpaired *t*-tests on their data, which were designed for repeated measures (analysis of variance). Nevertheless, the data were more compelling than in the earlier studies. Hissa et al. (1994) reported decreases of about 50% in total and free T<sub>3</sub> and T<sub>4</sub> in Finnish brown bears.

Baseline levels of thyroid stimulating hormone (TSH), a pituitary protein that induces release of T<sub>3</sub> and T<sub>4</sub>, were similar between dormant and active states (Azizi et al. 1979). However, the TSH response to thyrotropin-releasing hormone (TRH) during hibernation was prolonged and exaggerated relative to the active state. Triiodothyronine and T<sub>4</sub> increased with TRH challenge similarly in both seasons. These data led Azizi et al. (1979) to propose that bears have a hypothalamic hypothyroidism during hibernation. Function at the level of the thyroid gland is normoreactive, but reduced because of a deficiency of TRH.

At the level of the central nervous system, Franzmann et al. (1981) provided baseline serum levels of beta-endorphins, which are morphine-like peptides found in the brain and pituitary tissue of mammals, in hibernating and active bears. Hibernating black bears had higher levels of beta-endorphins than active black bears, active brown bears, and other non-hibernating mammals. Franzmann et al. (1981) cautiously suggested that because beta-endorphins can reduce blood pressure, respiration, body temperature, and metabolic rate, they may play a role in bear hibernation physiology. Recent data by Hissa et al. (1994), however, showed that beta-endorphin levels decreased during hibernation in brown bears. More work is needed in this area.

## Reproductive Physiology and Lactation

Reproductive function in male bears is quiescent during early hibernation (Garshelis and Hellgren 1994), but males are in or near reproductive readiness at the time of den emergence. Early studies of histology (Erickson et al. 1964) and serum testosterone (McMillan et al. 1976) suggested that testicular recrudescence begins before den emergence in black bears. Later work (Palmer et al. 1988, Garshelis and Hellgren 1994) with larger samples supported these contentions, as did observations that the pituitary and testis were most sensitive to gonadotrophin-releasing hormone during March (Horan et al. 1993). Similar results were observed in Hokkaido brown bears (*U. a. yesoensis*) (Tsubota and Kanagawa 1989). These data led Palmer et al. (1988) and Garshelis and Hellgren (1994) to proffer that photoperiod is the principal zeitgeber regulating male reproduction.

Elevated testosterone during hibernation may also play a nonreproductive function. Castration of 2 male bears during hibernation disrupted their physiology, resulting in defecation and urination. Restoration of testosterone with testosterone enanthate injections restored normal hibernation metabolism (Nelson et al. 1982).

Female bears exhibit the added phenomena of delayed implantation, gestation, and lactation during the hibernation period. Following conception in the summer breeding season, the fertilized egg arrests development at the blastocyst stage (about 300 cells). The unimplanted blastocyst remains dormant in the uterus until implantation in late November or early December (Wimsatt 1963). Parturition usually occurs in January or February (Alt 1983, Hellgren et al. 1991).

The American black bear and the brown bear exhibit similar reproductive endocrinology during hibernation. Serum concentrations of progesterone rise slowly through October and November prior to implantation. About 60 days prepartum, there is a sharp rise in serum progesterone concentrations (Foresman and Daniel 1983, Tsubota et al. 1987, Hellgren et al. 1991). This hormonal spike is concomitant with a marked alteration in corpora luteal morphology and a 2- to 4.5-fold increase in luteal volume (Wimsatt 1963). Tsubota et al. (1987) and Hellgren et al. (1991) reported gradual declines in progesterone concentrations after implantation to undetectable levels within 1–3 days postpartum. Most of these events occur during hibernation. Polar bears evince similar trends in serum progesterone during pre-implantation and at implantation (Palmer et al. 1988, Ramsay and Stirling 1988, Derocher et al. 1992); however, hormonal events in polar bears while hibernating have not been profiled.

The separation of the progesterone spike from denning in polar bears and observations that female black bears may remain active after implantation occurs (Hellgren 1988) suggests that hibernation metabolism and reproductive physiology are not directly linked (Palmer et al. 1988). However, Ramsay and Dunbrack (1986:735) proposed the intriguing hypothesis that bears produce neonates that are only a fraction of the mass predicted by allometric relationships for female mammals as an "adaptive response to physiological constraints associated with supporting fetal development while in a state of hibernation and without access to food." They suggested that bears shift from placental to mammary nourishment of their offspring during hibernation because of conflicting needs to conserve maternal protein while providing adequate energy substrates to neonates. Their hypothesis thus supports an evolutionary link between hibernation physiology and bear reproductive chronology.

Lactation in hibernating bears places unique metabolic demands on the female, as the first 2–3 months of maternal care occur during hibernation. Nutrients for neonatal growth must be supplied under conditions of no food and water. The fat content of polar and black bear milk is the highest known for terrestrial mammals, increasing from about 9% (on a wet-weight basis) immediately after birth to 30% in late lactation (Oftedal et al. 1993) in black bears. Milk from polar bears in the fourth month of lactation reached as high as 36% fat (Derocher et al. 1993). The pattern of milk energetics varied between polar bears that were on land (gross energy declined) and those on sea ice (energy remained steady), with variability believed to be associated with differential food availability in these environments. Protein content ranged from 5.9 to 12.6% in black bears and 9.1 to 13.2% in polar bears, while sugars comprised <5% of milk composition in both ursids (Derocher et al. 1993, Oftedal et al. 1993). The production of high-fat, low-carbohydrate milk is adaptive to the metabolic economy of hibernation, as it conserves maternal protein yet generates rapid neonatal growth.

Nelson's body of work (see Protein Metabolism above) attests that bears conserve protein during hibernation. However, this work was conducted with male bears. Obviously, gestating and lactating female bears cannot fully conserve protein stores, because of fetal and neonatal development. How large are the demands of lactation? Oftedal et al. (1993) estimated that a black bear cub requires about 11 kg of milk (composed of 7 kg water, 2.5 kg fat, 0.8 kg protein, and 0.25 kg total sugar) over their first 12 weeks of life to gain 2.5 kg. A female bear nursing a litter of 3 must therefore produce 33 kg of milk in those 12 weeks, during which time the family group is in the den. Although mothers can recover most of the water and about 50% of the nitrogen in protein by recycling (e.g., ingesting the excreta of the cubs), this represents about 7.5 kg of fat (2.5 kg  $\times$  3 young) and 1.2 kg of protein (0.8 kg  $\times$  3 young  $\times$  0.5 recovery) retained by this litter during denning.

Using estimates of body composition from Farley and Robbins (1994), a 100-kg female with 30% fat would contain about 15.5 kg protein. The lactational drain would be <10% of body protein mass. Body mass loss by 4 hibernating, lactating bears (litter size: 1–3) was 27% of body mass from initiation of hibernation at 3 January to 31 March, compared to 20% loss in 6 nonlactating females (Hellgren et al. 1990, E.C. Hellgren, unpubl. data). Atkinson and Ramsay (1995) estimated that polar bears lost 43% of body mass while fasting and lactating, with 93% of the energy expended drawn from fat stores.

## Serum Chemistry and Hematology

Many serum chemical characteristics vary between active and hibernating states, but remain stable during hibernation. Hellgren et al. (1990) reported that serum concentrations of calcium, sodium, potassium, chloride, and glucose did not vary ( $P < 0.05$ ) over a 6-month period that included fall hyperphagia and hibernation. Concentrations or activity of other chemicals differed between hibernation and active periods, but remained stable during hibernation, including alkaline phosphatase, alanine aminotransferase, total protein, globulin, albumin:globulin ratio, urea nitrogen, creatinine, and urea-creatinine ratio (Hellgren et al. 1990). Phosphorus showed an increasing trend during hibernation. These results were consistent with previous literature. Urea nitrogen and creatinine changes will be discussed below, while changes in other characteristics have been analyzed in earlier sections (see Protein Metabolism, Bone Metabolism, Fat Metabolism).

An annual cycle in hematological characteristics has been observed in several populations of black bears (Erickson and Youatt 1961, Franzmann and Schwartz 1988, Hellgren et al. 1989, 1993) and brown bears (Pearson and Halloran 1972, Hissa et al. 1994). During hibernation, the red blood cell population is composed of numerous small cells. Hemoglobin concentration, hematocrit, and red blood cell count peak during autumn hyperphagia and winter hibernation and decline to a nadir in summer (Hellgren et al. 1989). The shift to a smaller mean cell size during hibernation may be adaptive by increasing erythrocyte surface area and improving gas exchange efficiency (Matula et al. 1980). In autumn and winter, blood viscosity appears to be higher, which also may be adaptive to hibernation (Halikas and Bowers 1972).

Limited evidence suggests that immune function in ursids is depressed during hibernation. The population of white blood cells declines in bears during hibernation (Erickson and Youatt 1961, Hellgren et al. 1989, Hissa et al. 1994), and Karjalainen et al. (1995) found a reduced proliferative response of lymphocytes to antigenic stimulation during February and March, although T-cell reactivity to a mitogenic stimulus did not vary seasonally.

Serum chemical and hematological values may be used to assess nutritional condition of hibernating bears. DelGiudice et al. (1991) stated that hematologies may be sensitive to annual changes in nutritional status and may help examine effects of lactation. Hellgren et al. (1993) recommended the use of serum chemical and hematologic data from early hibernation, among other seasons, as a tool to assess annual differences in habitat quality. Noyce and Garshelis (1994) reported that mean corpus-

cular volume, serum creatinine, and total serum protein reflected condition in hibernating adult females, as their incorporation with body mass in regression models improved prediction of size and growth of young. However, they cautioned that blood variables are not reliable indicators of body condition and recommended further study of relationships between body condition and serum metabolites during hibernation.

### Urea:Creatinine Ratio

A consequence of ursid hibernation physiology, first reported by Nelson et al. (1983), is a decline in the ratio of serum urea to serum creatinine (U:C) concentrations in black bears from >20 during normal, active periods to <10 during hibernation. Changes in protein metabolism discussed above act to reduce serum urea concentrations, and thus the U:C ratio, during hibernation. The ratio also decreases during hibernation because of apparently obligate, 2- to 3-fold increases in serum creatinine concentrations during hibernation, also discussed above. It was subsequently hypothesized that black bears may begin entering the physiological state of hibernation weeks before actual denning behavior, based on U:C ratios <10 during late summer and fall (Nelson et al. 1984). They concluded that a U:C ratio <10 is a biological indicator of the hibernating state. Recently, using U:C ratio data, Ramsay et al. (1991) suggested that polar bears can facultatively adopt a physiological and biochemical state similar to hibernation during food scarcity. New data in Atkinson et al. (1996) implied that polar bears with adequate fat stores at the start of a fast avoided net catabolism of protein, and thus had low U:C ratios.

The work of Nelson et al. (1984) was followed by a flurry of papers and abstracts containing data on U:C ratios from black bears in several states (Ensrud et al. 1986, Schroeder 1987, Franzmann and Schwartz 1988, Storm et al. 1988, Hellgren et al. 1989, 1990). These papers generally supported the notion that the U:C ratio dropped below 10 in hibernating bears. Storm et al. (1988) extended these observations with the finding that U:C ratios of cubs, which averaged 29.0 and 22.8 for males and females, respectively, demonstrated that cubs in the den were not in the physiological state of hibernation.

We have argued (Hellgren et al. 1989, 1990) that variation in diets of free-ranging, active bears makes a ratio of these variables too simplistic to use as an indicator of the hibernating state. Although hibernating bears have been conclusively and repeatedly shown to have mean U:C ratios <10, bears with U:C ratios <10 are not necessarily in the hibernating state. Several black bear populations contain individuals with U:C ratios <10 during active feed-

ing periods (Virginia–North Carolina, Hellgren et al. 1989; Arkansas, Scott 1991; Florida–Mexico, Hellgren et al., In Press).

In a free-ranging bear population, the most obvious factor potentially affecting serum urea concentrations and the U:C ratio is diet, specifically protein intake. In several mammals, evidence of protein sparing during fasting or consumption of low-protein diets has been found in the form of decreased urea concentrations and U:C ratios (sometimes <10; Pfeiffer et al. 1979; Costa and Ortiz 1982; Lochmiller et al. 1985, 1986, 1988; DelGiudice et al. 1987, 1990) and urea recycling (Pernia et al. 1980, Riedesel and Steffen 1980). These data document that a U:C ratio <10 is not unique to hibernating bears and can result from decreased protein intake. I propose that low U:C ratios in black bears during late summer and fall (Nelson et al. 1984) are a direct result of feeding on low protein foods (Hellgren et al. 1989, Pritchard and Robbins 1990). The lack of a difference ( $P > 0.05$ ) in serum creatinine concentrations between summer and fall samples (Nelson et al. 1984) is further evidence that these animals had not entered hibernation mode, as creatinine is not affected by dietary protein content (Lochmiller et al. 1986, 1988) but is elevated in hibernation.

Black bears, northern elephant seals (*Mirounga angustirostris*), and black-tailed prairie dogs (*Cynomys ludovicianus*) appear to be seasonally restricted in their homeostatic responses to fasting (Nelson et al. 1975, Pfeiffer et al. 1979, Costa and Ortiz 1982), whereas it has been hypothesized that polar bears can facultatively enter the physiological state of hibernation during food scarcity (Nelson et al. 1983, Ramsay et al. 1991). Nelson et al. (1983) reported that U:C ratios and blood lipid concentrations of wild, active polar bears were similar to those of hibernating black bears and that polar bears were in walking hibernation, i.e., the biochemical state of hibernation while active. They concluded that polar bear behavior and biochemistry indicated a continuous ability to hibernate, winter or summer.

The polar bear hypothesis was supported by Bruce et al. (1990), who reported that thirteen-lined ground squirrels (*Spermophilus tridecemlineatus*) injected with blood from denning or nondenning polar bears in winter and spring hibernated with significantly more and longer hibernation bouts than squirrels injected with saline or blood from an active female polar bear from the fall. Ramsay et al. (1985, 1991) stated that U:C ratios also supported the hypothesis that polar bears can switch facultatively to a hibernation-like state in response to food shortages. Presentation of separate frequency data for serum urea and creatinine concentrations, as for U:C val-

ues in Ramsay et al. (1991: Fig. 1), would permit insight into whether polar bears are physiologically hibernating (decreased urea, elevated creatinine) or merely fasting with protein sparing (decreased urea, unchanged creatinine) during summer and fall food scarcity (Derocher et al. 1990, Atkinson et al. 1996). Low U:C ratios in polar bears on the sea ice also may result from the tendency of polar bears to consume lipid depots of their prey but not muscle mass (Stirling and McEwan 1975). Animals on a high-lipid, low-protein diet would have low serum urea levels and thus a low U:C ratio.

I conclude that the U:C ratio is not a reliable index of the hibernating state in bears. As mentioned by Hellgren et al. (1989, 1990), more controlled experimental work is necessary to elucidate the relationships among the U:C ratio, the hibernation state, and dietary protein intake in ursids. More study also is necessary to elucidate the cause for the 2- to 3-fold rise in serum creatinine during bear hibernation.

Polar bears may indeed be able to switch to a state of facilitated fasting in response to an absence of food resources, though perhaps the physiology of active-fasting and denning-hibernating polar bears represents separate metabolic states. Nevertheless, the U:C ratio does not contain sufficient information to use alone as an indicator of hibernation. More detailed metabolic and behavioral study is necessary to answer this question in polar bears, as stated by Nelson et al. (1983).

## NEW FRONTIERS AND RESEARCH NEEDS

Evidence for a substance that induces hibernation, termed the hibernation induction trigger (HIT), was first presented by Dawe and Spurrier (1969). Recently, plasma or the albumin fraction of plasma from hibernating black bears (Ruit et al. 1987) and polar bears in a variety of states (winter and spring, denning or nondenning; Bruce et al. 1990) induced hibernation in thirteen-lined ground squirrels. More detailed work suggested that the trigger substance is an endogenous opioid produced by hibernating bears, but in reduced amounts by summer- and winter-active individuals (Bruce et al. 1992, 1996). However, plasma injections from hibernating brown bears did not induce metabolic suppression in Djungarian hamsters (*Phodopus sungorus*) or laboratory rats (Karjalainen et al. 1994). Karjalainen et al. (1994) concluded that no universal and transferable HIT occurs in brown bear plasma. Interspecific inductions of hibernation have only been successful in thirteen-lined ground squirrels, which have also hibernated in response to a variety of non-specific stimuli (Wang et al. 1988), suggesting that they may

not be a good model species for this line of research. On the other hand, hamsters and rats do not hibernate, and thus may not possess appropriate receptors to a HIT substance.

Hibernation research continues in clinical, evolutionary, and physiological arenas. Clinical applications have been provided in the areas of renal disease, obesity, and anorexia nervosa (Nelson 1987). The studies of Floyd et al. (1990) have potential application to osteoporosis and other bone maladies. Isolation of a HIT may provide a way to lengthen preservation time of major organs and organ systems for transplantation (Chieh et al. 1991).

The adaptive significance of hibernation and its impact on life-history strategies of bears will continue to stimulate research (Ramsay and Dunbrack 1986). Many critical topics remain un- or underresearched. I again thank M.A. Ramsay for providing a laundry list of important questions relative to ursid hibernation. For example, virtually nothing is known about hibernation and reproduction in tropical bears. Are females in the tropical species constrained to fast after parturition because of the altriciality of the young? Limited evidence suggests that this is the case in sloth bears (*Melursus ursinus*; M. A. Ramsay, Univ. Saskatchewan, Saskatoon, Sask., Canada, in litt., 1996). Physiologically, is this the same state as in temperate bears? In hibernating, temperate species, do physiological parameters of hibernation vary clinally with hibernation duration? Additional study is warranted on the feats of gestation and lactation in female bears without food or water. Environmental contaminants may have unique effects on hibernating bears. Accumulated, fat-soluble biocontaminants that are released during fat catabolism in hibernation may affect early embryonic growth and development and future reproduction in bears feeding high in the food chain, such as polar bears and coastal populations of brown bears. Neural controlling mechanisms and processes of hibernating bears are a fertile area of research and may have clinical applications for metabolic problems.

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