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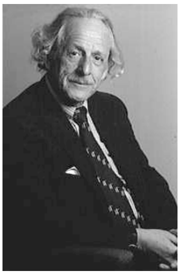

Current Comments®

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# Nothing to Snooze At: Exploring the Mysteries of Hibernation

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Hibernation, a form of cold-adaptation found primarily in mammalian species, involves marked declines in body temperature, heart rate, respiration, and metabolic rate. We have identified several ISI® research fronts related to hibernation, including thermogenesis (heat production), thermoregulation, and other forms of cold-adaptation. Many aspects of hibernation remain unexplained, and researchers continue to investigate its effects, as well as potential biochemical applications.

For humans in the developed world, getting through the winter months has largely become a matter of inconvenience and expense rather than one of survival. For animals in the wild, of course, the situation is entirely different. Adaptation to the extreme conditions of winter in the middle and high latitudes is essential to survival. In the face of harsh temperatures and scarce food supplies, some animals have adapted by hibernating.

The most popular conception of hibernation probably involves a bear slumbering its way through the winter in a cozy den. While accurate to a point, this picture does not convey the full complexity of the physiological mechanisms involved in hibernation. Because many of these mechanisms are still not completely understood, researchers continue to investigate various aspects of hibernation. Their work may one day have clinical applications in many fields.

Using the ISI® databases, we have identified research activity in a number of areas related to hibernation. These include research in thermogenesis (heat production), thermoregulation, and other aspects of cold-adaptation.

## Definitions and Behavioral Aspects

The word "hibernation," derived from the Latin *hibernus*, meaning "of winter" or "wintry," encompasses various terms and behaviors. As discussed by Charles P. Lyman, Department of Anatomy, Harvard Medical School, Boston, Massachusetts, the verb "to hibernate" in its common usage means "to pass the winter in a torpid or lethargic state."[1] The broad sense of the word could apply to reptiles, amphibians, fish, invertebrates, and even many plants. Hibernation in mammals and birds, however, is a more specific subject—one that is "inextricably bound up with the phenomenon of warm-bloodedness and the control of body temperature."[1]

Wilma A. Spurrier, Division of Neurosurgery, Loyola University, Maywood, Illinois, and colleagues refer to hibernation as "a striking circannual rhythm that is physiologically characterized by regulated declines in body temperature, respiration, heart rate, metabolic rate, and food consumption."[2] Ralph J. Berger, Department of Biology, University of California, Santa Cruz, characterizes hibernation as a physiological adaptation that enables warm-blooded animals to cope with periodic limitations in energy supplies through reductions in body temperature and metabolism.[3] Berger distinguishes two forms of this adaptation. One is "shallow torpor," which is exhibited by some birds and many small mammals. This state is characterized by a decrease of about 5 to 20 degrees Celsius in body temperature, a quiescent, supine posture, and diminished responsiveness to the environment. Berger notes that shallow torpor usually occurs within the normal major sleep period but sometimes extends over multiday episodes. When it occurs in hotter, drier portions of the year, this type of shallow torpor is known as "estivation."[3]

In contrast to shallow torpor, Berger refers to hibernation as "deep torpor," practiced by only a few species within one-third of the mammalian orders. Hibernation is characterized by more profound decreases in body temperature and responsiveness than shallow torpor. This deep hibernation occurs during the cold seasons of the year.[3]

As Lyman notes, mammals that undergo deep hibernation include dormice, ground squirrels, chipmunks, prairie dogs, marmots, woodchucks, some species of bats, and deer mice.[4]

Reviewing various aspects of mammalian hibernation, Lawrence C.H. Wang, Department of Zoology, University of Alberta, Edmonton, Canada, notes that a bout of hibernation consists of entry, maintenance, and arousal, followed by a brief period of euthermic (warm-blooded) activity before another bout of hibernation begins.[5] The hibernation season of an animal may extend from September to March, consisting of several hibernation bouts, each lasting from a few days to several weeks.

As Wang notes, it is unclear and somewhat puzzling why hibernators undergo periods of spontaneous arousal, particularly in view of the high energy costs associated with arousal and euthermic activity.[5] The explanation seems unrelated to the need for food or for the elimination of metabolic wastes. Alan R. French, Department of Biology, University of California, Riverside, suggests that arousals are initiated by some chemical imbalance that develops while hibernators metabolize at low body temperatures. Evidence indicates that the animal must metabolize at a higher body temperature for short periods in order to restore homeostasis—that is, an internal constancy and stability that is independent of the environment.[6]

## Physiological and Neural Aspects

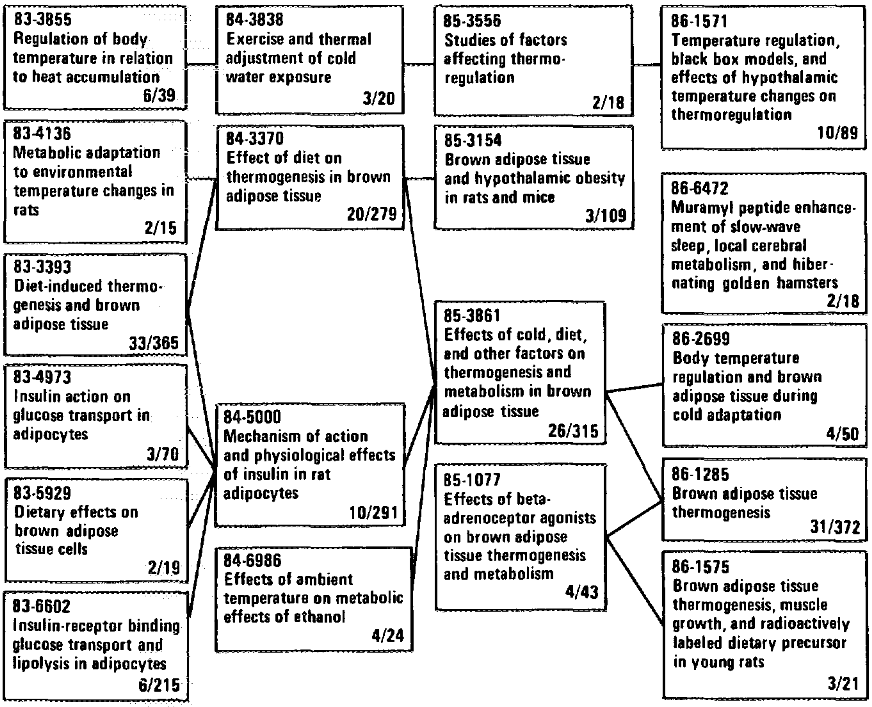
As Lyman notes, "the factors which permit or cause an animal to enter hibernation are not well understood."[7] He reviews studies on the pharmacological aspects of various hibernation states, including the role of catecholamines and other neurotransmitters in the hibernation cycle.

In another review Roland C. Aloia, Department of Anesthesiology, Loma Linda University School of Medicine, California, discusses a basic question concerning mammalian hibernation: the mechanisms of membrane adaptation, which permit the continued functioning of cell membranes at low temperatures. As Aloia notes, the exact mechanisms that permit this function are unknown but seem to be related to the fluidity of the membrane and to the level of membrane fatty acids. Unsaturated fatty acids have been found to enhance membrane fluidity at low temperatures, although there does not appear to be a consistent trend toward greater levels of unsaturated fatty acids in the tissues of hibernating animals. According to Aloia, the precise role of membrane fatty acids in mammalian hibernators during their hibernation state remains to be explained.[8]

Fritz Geiser and G.J. Kenagy, Department of Zoology, University of Washington, Seattle, found that chipmunks fed a diet rich in polyunsaturated fats had longer bouts of hibernation with lower body temperatures and lower metabolic rates than chipmunks on a diet of saturated fatty acids. These results, the authors concluded, provided clear evidence that membrane fatty acids influence regulation of body temperature in a mammal at low temperatures.[9]

H. Craig Heller, Department of Biological Sciences, Stanford University, California, discusses the neural aspects of hibernation. The central nervous system's thermoregulatory system, largely concentrated in the area of the brain known as the hypothalamus, is not *inactivated* during hibernation—it is reset to a lower level. This broadband "thermostat" of the hibernator shows a gradual suppression of "set point" during entrance into a bout of hibernation. Hypothalamic temperature is the main feedback signal to this regulator of body temperature, and if the hypothalamic temperature falls below "set point" during hibernation, the animal increases its heat production and avoids freezing. How could this broadband thermostat have evolved? During slow-wave sleep there is a similar but lesser downward resetting of the hypothalamic thermostat. In

**Figure 1:** HIBERNATION AND BROWN ADIPOSE TISSUE. Historiograph tracing developments in this research. Numbers of core/citing papers are indicated at the bottom of each box.




other experiments it is shown by EEG recordings that animals enter hibernation through slow-wave sleep. Hence, hibernators would have evolved through natural selection favoring the energy conservation due to lower and lower regulated body temperatures during slow-wave sleep. Heller speculates on a neural circuit that might be responsible for regulatory cycles of sleep/wakefulness and hibernation/euthermia.[10]

## Research Fronts Highlight Studies of Brown Adipose Tissue

A wide variety of research fronts pertaining to hibernation can be found in the historiograph in Figure 1. In 1986 Heller was identified as one of two core authors in the front concerning "Muramyl peptide enhancement of slow-wave sleep, local cerebral metabolism, and hibernating golden hamsters," #86-6472. There are 18 citing papers in this front.

Many of the fronts in Figure 1 concern brown adipose tissue. As Björn A. Afzelius, University of Stockholm, Sweden, notes, brown adipose tissue has been the subject of research for over 300 years. Also referred to as brown fat, multilocular adipose tissue, and hibernation gland (among other terms), brown adipose tissue is regarded as a "thermogenic effector"—a tissue with the function of heating the blood passing through it.[11] It is found in hibernating and nonhibernating mammals (including humans) and is associated with a form of heat production referred to as "nonshivering thermogenesis."

Speculation has centered on the role of brown adipose tissue in hibernation, particularly in heat production prior to arousal periods. Lyman and Harvard colleague Regina C. O'Brien, after removing the brown adipose tissue from ground squirrels and hamsters, conclude that this tissue is involved in, but not essential to, hibernation.[12]

W.P.T. James, University of Cambridge, and P. Trayhurn, Addenbrooke's Hospital, Cambridge, UK, review thermogenesis and obesity in animals and humans. In humans the authors note a relationship between brown adipose tissue metabolism, food intake, and body weight. In experiments where subjects consumed excessive amounts of a high-fat diet, thin subjects seemed to display greater thermogenesis—that is, an ability to burn the excess energy and maintain a lower body weight. The exact role of brown adipose tissue in human obesity and thinness, however, remains uncertain.[13]

Thirty-one core papers and 372 citing papers identify a 1986 research front on "Brown adipose tissue thermogenesis," #86-1285. Four of these core documents were written by Nancy J. Rothwell and Michael J. Stock, Department of Physiology, Queen Elizabeth College, University of London, UK. One of these papers is "A role for brown adipose tissue in diet-induced thermogenesis," a 1979 article from *Nature*. In this study the authors examined thermogenesis and energy balance in rats during voluntary overeating. Rothwell and Stock conclude that brown adipose tissue may determine metabolic efficiency and resistance to obesity.[14]

Three of the core documents in front #86-1285 were written by David G. Nicholls, Neurochemistry Laboratory, Department of Psychiatry, Dundee University, UK. One of these papers, "Thermogenic mechanisms in brown fat," from *Physiological Reviews*, was coauthored in 1984 with colleague Rebecca M. Locke. In this review, the authors examine various cellular processes associated with thermogenesis, including respiratory response of brown fat cell, fatty acid activation and oxidation, and plasma membrane depolarization.[15]

## Bear Hibernation

Hibernation in the black bear has been extensively studied and provides an interesting physiological model. Reviewing hibernation in the black bear and polar bear, Ralph A. Nelson, Department of Research, Carle Foundation and University of Illinois College of Medicine, Urbana-Champaign, refers to these animals as "metabolic marvels." As Nelson notes, during hibernation the black bear does not eat, drink, urinate, or defecate for five months or more. The bear burns up to 4,000 calories a day. Cubs are born and nursed during this time.[16]

Evidence demonstrates that the black bear is able to increase its body protein during hibernation. The bear's metabolism prevents the accumulation of such waste products as urea, which would otherwise cause fatal uremia. As Nelson points out, net formation of protein and prevention of uremia result from physiological mechanisms that shuttle nitrogen into protein.[16] Bears may refrain from eating or drinking for about three weeks after leaving their dens. It seems that the period of adaptation that frees the bear from the need for food and water begins before the bear enters its den for the winter and persists afterward.[17]

As Nelson notes, the study of bears has engendered differences of opinion as to whether bears are actually hibernators. They do not undergo periodic arousals, as deep hibernators do, and they remain relatively alert in their dens. Nelson concludes that they may *not* be hibernators.[16]

## The Search for a "Trigger"

While many aspects of hibernation remain mysterious, researchers continue to explore why and how animals enter and maintain this state. One factor that has received considerable attention is a biochemical "trigger" that seems to play a crucial role in hibernation.

In a 1968 experiment, Albert R. Dawe, Physiology Department, Stritch School of Medicine, Hines, Illinois, and Spurrier transfused blood from a hibernating ground squirrel into active squirrels under laboratory conditions.[18] Placed in a cold room, the active squirrels began to hibernate within 48 hours, even though the season was spring, a time when these animals do not enter deep torpor. By serially transfusing blood from the hibernating animals into active ones, the researchers were able to continuously maintain hibernation in the colony of squirrels throughout spring and summer—normally a time of activity for the ground squirrels. In late summer, the squirrels in the colony began their naturally occurring, spontaneous hibernation cycle, ending the experiment.

As the authors observed, these results indicated a "trigger" for natural mammalian hibernation, carried in the blood.[18] In subsequent experiments, Spurrier, Dawe, and others have attempted to isolate and characterize this substance, which has become known as the "hibernation trigger" (HT) or "hibernation induction trigger" (HIT).

R.D. Myers, Departments of Psychiatry and Pharmacology, University of North Carolina School of Medicine, Chapel Hill; Peter R. Oeltgen, Veterans Administration Hospital, Lexington, Kentucky; and Spurrier injected serum albumin extracts from the blood of hibernating woodchucks into macaque monkeys, which are normally incapable of entering into hibernation. After the injections, the monkeys—placed in restraining chairs with their vital signs closely monitored—showed reductions in body temperature, food intake, and heart rate. The authors noted that this was the first demonstration that a plasma "trigger" factor exerted a direct physiological action on the brains of nonhibernating mammals.[19] In a subsequent experiment, with colleague R.A. Blouin, College of Pharmacy, University of Kentucky, Lexington, the authors noted that plasma from hibernating woodchucks had a similar effect on rhesus monkeys. Apart from the reductions in body temperature, heart rate, and appetite, the trigger also exerted an action on the kidneys of the primates. This suggested, according to the authors, that the trigger directly altered the glomerular filtration and tubular reabsorption processes in the kidneys of the primates in a manner that matched descriptions of other species during hibernation.[20]

Myers and colleague T.L. Yaksh are coauthors of a 1969 paper, "Control of body temperature in the unanaesthetized monkey by cholinergic and aminergic systems in the hypothalamus."[21] This is one of seven core documents identifying a 1985 research front, "Central effect of angiotensin, catecholamines, and other neurotransmitters on hypothalamic thermoregulatory responses and body temperatures," #85-2731.

Researchers have attempted, without complete success, to isolate the trigger factor. Oeltgen and Spurrier, after applying a variety of techniques, characterized the trigger molecule as a small protein, closely associated with albumin.[22] In another experiment Oeltgen and colleagues (including Spurrier and Myers) injected monkeys with blood from hibernating woodchucks and observed the same inhibitory effects on body temperature, appetite, and heart rate. The monkeys remained in an anesthetizedlike state for several hours. The sedated behavior of the primates infused with HT suggested the behavior of monkeys injected with morphine or other opiates. The authors then administered the opiate antagonists naloxone and naltrexone, which either reversed or retarded these effects in the monkeys. The authors hypothesized that the trigger fraction from the hibernating woodchucks serves as a carrier for a potent opiatelike substance. This opioidlike peptide, they concluded, may be unique to the hibernator.[23]

Researchers are continuing their efforts to isolate HIT and explore its relationship to opioids and opioid receptors—although, as Oeltgen and colleagues point out, the exact mechanism by which the trigger induces hibernation is unknown.[24] In fact, the very existence of a trigger is not a matter of unanimous agreement among researchers. Wang, for example, points to a recent experiment in which he and his colleagues were unable to find conclusive evidence of an HIT in the Richardson's ground squirrel. Results also cast doubt on the validity of the 13-lined ground squirrel as a standard test animal for the bioassay of the trigger substance.[25] Like many other aspects of hibernation, this is a matter requiring further research.

In Table 1 we present a list of organizations concerned with research on hiberna-

**Table 1:** HIBERNATION ORGANIZATIONS. Selected list of organizations concerned with research on hibernation.

American Society of Zoologists
P.O. Box 2739
California Lutheran College
Thousand Oaks, CA 91360

International Association for Bear Research and Management
P.O. Box 3129, Station B
Calgary, Alberta T2M 4L7
Canada

International Hibernation Society
300 Dean Drive
Rockville, MD 20851

Society for Cryobiology
c/o Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, MD 20814

**Table 2:** SELECTED LIST OF JOURNALS THAT PUBLISH ARTICLES ON HIBERNATION. A=title, first year of publication, and publisher. B=1986 impact factor. C=number of articles on hibernation covered between 1984 and 1987 in *SCISEARCH®*. D=total number of articles in each journal covered in *SCISEARCH* between 1984 and 1987.

| A | B | C | D |
|---|---|---|---|
| American Journal of Physiology (1898) American Physiological Society Bethesda, MD | 0.50 | 10 | 5,891 |
| American Zoologist (1961) American Society of Zoologists California Lutheran College Thousand Oaks, CA | 2.53 | 10 | 2,057 |
| Canadian Journal of Zoology (1929) National Research Council of Canada Ottawa, Canada | 0.86 | 8 | 1,714 |
| Comparative Biochemistry and Physiology. Part A—Comparative Physiology (1961) Pergamon Press Elmsford, NY | 0.78 | 14 | 1,619 |
| Comparative Biochemistry and Physiology. Part B—Comparative Biochemistry (1961) Pergamon Press Elmsford, NY | 0.78 | 6 | 1,734 |
| Cryo-Letters (1979) Cryo-Letters Cambridge, United Kingdom | 0.86 | 6 | 204 |
| Cryobiology (1964) Academic Press New York, NY | 1.42 | 27 | 705 |
| Journal of Comparative Physiology B (1924) Springer-Verlag New York, NY | 0.51 | 5 | 286 |
| Journal of Thermal Biology (1976) Pergamon Press Elmsford, NY | 0.69 | 14 | 211 |

tion. Table 2 is a list of journals that publish hibernation research. According to data from the *Science Citation Index®*, there were about 2,500 articles published explicitly on hibernation (approximately 1,145 articles) and brown adipose tissue (1,350 papers) between 1974 and 1987. The 245 articles published on these topics in 1987 represent a twofold increase over the 127 papers that appeared in 1974.

## Theories of Hibernation

In addition to exploring the physiological and biochemical components of hibernation, researchers have theorized about its more general aspects. One of these aspects concerns hibernation's relationship to sleep. Berger[3] and Heller,[10] for example, have noted that slow-wave sleep, shallow torpor, and hibernation are homologous states. Berger and colleague James M. Walker review correlations between sleep, body temperature, and thermoregulation. They speculate that deeper states of dormancy, including hibernation, evolved through a gradual extension of thermoregulatory adjustments initiated in all mammals during sleep.[26]

H. Pohl, Max Planck Institute for Behavioral Physiology, Andechs, and H. Giedke, Center for Psychiatry and Neurology, Tübingen, Federal Republic of Germany, investigated the hypothesis that hibernation is analogous to seasonal affective disorder (SAD) in humans. In their experiment the antidepressant lithium was found to delay or suppress natural hibernation in hamsters. This indicated, as the authors note, "a direct effect of lithium on functions essential to the expression of torpor." Hibernation, they concluded, may be an animal model for seasonal depression in humans, apparently involving similar mechanisms of internal circadian rhythm and neurotransmitter function.[27] We discussed SAD in our recent essay on chronobiology.[28]

## Potential Applications

As research continues into hibernation and more is understood about its various mechanisms, the results will likely have ramifications in many fields. Since hibernation appears to be an evolutionary extension of normal mammalian sleep, it is a valuable model system for studying the neurobiology of arousal-state control. Oeltgen and Spurrier observe that, because animals other than hibernators have been shown to respond to the hibernation "trigger" molecule, the clinical potential of this molecule is great.[22] As they point out, studies have demonstrated that hibernating hosts display increased resistance to microbial infection. Under experimental conditions hibernating mammals have also displayed an increased resistance to the development of sarcoma and to potentially lethal doses of radiation. Oeltgen and Spurrier call for more research into a possible role for the induction trigger in organ preservation and transplantation, cryosurgery, tumor inhibition, and dietary control.[22]

As Nelson notes, data on water and protein metabolism in the bear have been applied in a program designed to save time and money spent on hemodialysis for humans awaiting kidney transplants. With careful control of the patients' water and protein intake, hemodialysis could be postponed for up to 10 days. Nelson speculates that principles gleaned from bear research might also be applied someday in long-duration space flight.[29]

Further research into hibernation will cast more light on these possible applications, as well as on the numerous questions still surrounding this intriguing form of adaptation.

* * * * *

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