Hibernation in Mammals

By Charles P. Lyman, A.B., M.A., Ph.D.

Hibernation and enforced hypothermia in mammals are widely different physiologic states. Prior to hibernation there are various preparations for the hibernating state, including polyglandular endocrine involution, fattening and/or food storage, and changes in the saturation of depot fat in some animals. The actual causes for the onset of hibernation are unknown, for most hibernators can remain active at low environmental temperatures for long periods. Entrance into hibernation is under precise physiologic control, with heart rate, respiratory rate, and oxygen consumption slowing before a decline in body temperature. A reasonably high blood pressure is maintained during this period and in deep hibernation by an increased peripheral resistance produced in part by vasoconstriction. Homeostasis is continued in hibernation, as evidenced by a normal blood pH, a sensitivity to inspired CO₂, and a response to ambient temperature below 0 C. by increased metabolic rate. At any time during entrance into hibernation or during hibernation the animal may arouse from this condition. Arousal is a coordinated physiologic event in which the anterior of the body is warmed rapidly by shivering and other heat generating mechanisms, while warmed blood is shunted from the posterior by differential vasoconstriction until the anterior reaches nearly 37 C. The tissues and organs of mammals that hibernate are capable of useful function at lower temperatures than the tissues of mammals that do not hibernate, but a hypothermed mammal that can hibernate will die in hypothermia even though it lives longer and at a lower temperature than a mammal that cannot hibernate. Hibernation must involve a resetting of the "physiologic thermostat," which thus permits a controlled cooling of the animal, but the nature of this "resetting" is not known.

The burgeoning interest in hypothermia for surgery has aroused some curiosity among physicians in the natural hypothermia that occurs seasonally in mammals that hibernate. There can be no doubt that natural hibernation as practiced by many bats, rodents and insectivores is a far less traumatic experience than the hypothermia that is forced on experimental animals, and a study of the former may help to clarify difficulties encountered in the latter. Quite obviously, both hibernation and hypothermia have in common a profound lowering of the usual body temperature of about 37 C., but, beyond this similarity, it is apparent that hibernation in all its phases is a controlled and remarkably regulated condition, while hypothermia consists virtually in a breakdown of temperature regulation that causes a weakening or collapse of other homeostatic mechanisms.

It has often been stated that mammals which hibernate have an inadequate system of temperature regulation so that, when exposed to cold, their temperatures decline and the animals enter the hibernating state. Actually, however, most hibernators that are not prepared for hibernation can stay active and healthy for months or even years at temperatures that are often fatal to the common laboratory animals of the same size. If, on the other hand, the potential hibernator is prepared for hibernation at the time it is exposed to cold, it may enter the state of hibernation within 24 hours.

Preparation for Hibernation

The nature of this preparation for hibernation is not clearly understood, but it is certain that the animal must be ready for hibernation or it will not hibernate. Most of the ground squirrel family become extremely

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From the Department of Anatomy, Harvard Medical School, Boston, and the Museum of Comparative Zoology, Harvard University, Cambridge, Massachusetts.

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fat as the season for hibernation approaches, but this does not necessarily seem to be correlated with an abundance of succulent foods. There is some evidence that the fatter animals hibernate before the thin ones, but, fat or thin, they all eventually hibernate during the fall months, and come out of the hibernating phase of their yearly cycle when spring arrives. The length of daily illumination has little, if any, effect upon this cycle, and the evidence to date indicates that the cycle is innate and receives few, if any, clues from the environment.2

Unlike the ground squirrels, the golden hamster is not truly cyclic and, if exposed to cold for sufficient time, will enter hibernation at any time of year. Hamsters store large quantities of food prior to hibernation. If denied the ability to store, hibernation is delayed, as if there were some safety check that will not permit the animal to hibernate without adequate supplies for the winter.3 Hamsters lose fat when exposed to cold prior to hibernation, and the fat that remains is less saturated and hence has a lower melting point than the fat from animals kept in a warm environment (fig. 1*).4 This would seem like a nice mechanism to maintain fat in a liquid condition during hibernation, but we have been able to show, in both hamsters and ground squirrels, that hibernation is not delayed when animals are fed a diet that results in depot fat so saturated that it is actually solid in the hibernating animal. Contrariwise, the onset of hibernation is not accelerated if the animals are fed a diet that results in body fat with a low melting point.

In the small rodent hibernators, lack of nourishment may rapidly induce hibernation. The metabolic budget of a diminutive mammal is extreme, for the high surface-to-mass ratio results in a disproportionately large heat loss. When denied metabolic fuel, the North American pocket mouse (Perognathus) enters the hibernating state and thus reduces its immediate metabolic problem.5 This is indeed a hibernation of desperation, for the food supply may be as bad when they awaken as when they entered hibernation. Other small hibernators, notably bats and the European birch-mouse (Sicista)6 usually allow their body temperature to drop any time they become inactive, though on other occasions they remain warm.

Apart from the condition of the animal as far as available food is concerned, there is evidence that the endocrine glands play a role in the preparation for hibernation. Histologic studies have shown that prior to hibernation all the endocrine glands show a marked decrease in activity. Hence it has been postulated that a polyglandular involution must take place before the animal can hibernate.7 The precise importance of the various endocrines in setting the stage for hibernation has not been elucidated, and some of the observed endocrine involution may be simply incidental. For example, the gonads of most hibernators involute right after the breeding season, which is several months before hibernation occurs. Moreover, it seems reasonably certain that no single endocrine

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gland controls the hibernating state, for removal of any one of them does not hasten the onset of hibernation.

**Hibernation**

In spite of its importance in the study of hibernation, the process of entering the hibernating state has been poorly understood. This is because the onset of hibernation is capricious and recording of the various changes involves instruments that can monitor a chronic preparation over long periods. Such instruments were unavailable a decade ago. It is natural to assume that a decline in body temperature would be the first indication of hibernation and that other vital functions would diminish in rate according to the van’t Hoff rule as the temperature dropped. Such is not the case, for respiratory rate, heart rate and oxygen consumption are all reduced before a detectable drop in body temperature occurs (fig. 2*). The contrast between this and enforced hypothermia is striking. In the hibernating animal, hibernation occurs passively as if, as Prosser has so aptly stated, someone had "turned down the thermostat." In enforced hypothermia the animal chills in spite of a violent metabolic effort to remain warm.

The actual entrance into hibernation is under fairly rigid physiologic control, and the decline in body temperature is always slower than it would be if the "thermostat" were quickly changed from a setting of 37 to 5 C. In most of the hibernators, bouts of shivering, often accompanied by gross muscular movements, take place from time to time. On these occasions the heart speeds and the metabolic rate increases. If the bouts are of long duration, the body temperature ceases to drop and often rises transiently. The result is that the animal may enter hibernation by uneven steps rather than in a smooth curve. At least one hibernator, the California ground squirrel, allows its body temperature to drop only part way toward the deeply hibernating state on its first attempt. With each subsequent entrance, the body temperature drops to a lower level, until it finally reaches a body temperature slightly above the ambient temperature of 5 C. (fig. 3†). It has been suggested that these precisely regulated drops serve to test the state of the animal, so that it never

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lowers its body temperature below a level for which it is physiologically prepared. Furthermore, each entrance into and arousal from hibernation in this animal takes place at a precise time of day, even in the absence of external clues, which suggests that the onset of hibernation is being controlled by some sort of an internal clock.

The circulation during entrance into hibernation in the thirteen-lined ground squirrel is regulated with considerable precision. The first precipitous decline in heart rate, signaling the start of the whole process, causes a drop in blood pressure which, however, remains within the normal values for active animals (fig. 4*) The heart continues to slow, both by skipping beats and by reduction in the number of even beats (fig. 5). As hibernation deepens, this becomes more and more exaggerated until, in deep hibernation, the heart rate can be as low as 3 beats a minute, with periods of bradycardia lasting 30 seconds or more (fig. 6). Peripheral resistance, as indicated by the slope of the diastolic runoff, increases with the decline in body temperature, so that the mean blood pressure remains at remarkably high levels for such a slow heart rate. Undoubtedly part of the increase in peripheral resistance is due to the increased blood viscosity at low temperatures, but some of it must also be caused by vasocostriction, for vasodilators and adrenergic blocking agents cause a decrease in peripheral resistance accompanied by an increase in heart rate that may be in part compensatory (fig. 7). Since the temperature in every part of the body declines at an equal rate (see figs. 2 and 4), it is apparent that the vasocostriction is generalized, and not confined to certain organs or areas.10

The preferential ambient temperature for hibernation in most mammals is a few degrees above the freezing point of water. As the body temperature approaches that of the environment, the body temperature curve be-


Figure 3

Brain temperature of a California ground squirrel entering hibernation in the cold during the summer, showing 3 test drops. M and N=midnight and noon. (From Strumwasser.)
times the animal remains in hibernation with a higher metabolic rate, and on other occasions the metabolic effort is sufficient to cause arousal from hibernation. In other cases this rather low-grade temperature regulation is insufficient to protect the animal, and it freezes to death in hibernation.11

Deep hibernation does not last throughout the winter in any mammal, for periodically the animal wakes, eats stored food if available, voids, and returns to the hibernating state. The periods of arousal vary with the species. Hamsters generally hibernate for only 3 to 5 consecutive days, ground squirrels for a few days longer, and bats may hibernate for a month or more without waking.

During the periods of hibernation, cell growth and replacement are greatly reduced but not completely stopped. Although it has been reported that mitotic activity is in abeyance during hibernation,12 we find mitotic figures in the crypts of Lieberkühn of ground squirrels that have been hibernating continuously for as long as 13 days. Radioactive iron, injected into continuously hibernating hamsters, is found in the erythrocytes, showing that hematopoiesis is continuing, albeit at a very slow rate. The reduced rate of cell production seems to be paralleled by a slow rate of cell aging and destruction, for erythrocytes tagged with chromium remain in the circulation for a much longer time in a hibernating animal than they do in an animal that is active.13 No experiment has been designed which proves that an animal in hibernation lives longer than its active litter mate.

Figure 4
Blood pressure (mm. Hg), heart and abdominal temperature and heart rate of a thirteen-lined ground squirrel entering hibernation. Blood pressure in dark area is highest systole and lowest diastole recorded for a 1-minute period at 5-minute intervals. Heart rate and blood pressure decline before body temperature. Heart remains slightly warmer than abdomen in hibernation. (From Lyman and O’Brien.10)

Figure 5
A. Blood pressure and EKG of animal graphed in figure 1. Uneven pattern of beats is typical for this stage. 4:26 p.m. = 1½ hours on figure 1. B. Same animal later. Pattern of beats and skipped beats is now even. (From Lyman and O’Brien.10)
but it is interesting that bats, which may spend one-half of their life in hibernation, are extremely long-lived animals for their size.

Earlier clinical work had suggested that neoplastic tissue might be differentially killed or its growth slowed by cold, and hibernating animals provided an excellent opportunity to test this premise. Homologous tumors implanted in the cheek pouch of hamsters which then enter hibernation showed no detectable increase in size during the period of hibernation, though on microscopic examination some of the cells appeared to be viable. As soon as the animals awoke from hibernation, however, growth of the tumors resumed. Heterologous human tumors, implanted in the same manner, also were not destroyed by the 5 C. temperature of hibernation and lived to grow again when the animals awoke.

Animals exposed to radiation during hibernation show little or no cellular damage as long as they remain in the hibernating state. Once they have aroused from hibernation, the cell destruction begins and the length of the animal's life is only prolonged by the number of days it has been in hibernation. The nature of this "radiation memory" is not understood, and its study may be a help in the clarification of the processes involved in radiation injury. Reparative processes, such
as hematopoiesis after bleeding, take place at an extremely slow rate, if at all, during hibernation and it is only after waking that the animal reacts to the stimulus for repair (fig. 8*).

Arousal

Continuous hibernation throughout the winter months would be the most efficient way to avoid an unfavorable situation, but this does not occur in any species that has been studied. Although many theories have been advanced, the cause for periodic arousals is not understood. Arousal may be evoked from an animal in hibernation at any time if a sufficiently strong stimulus is applied, but the strength of the stimulus necessary to produce the arousal seems to vary with the species and the physiologic state of the animal at the time. The process of arousal is a coordinated series of physiologic events in which the hibernator returns to the active state in a minimum of time using only heat generated by its own body. In this orderly sequence, the control of the circulation is remarkably exact, and it is this circulatory control that permits the rewarming with such efficiency. Arousal from hibernation is in sharp contrast to the condition of an animal in enforced hypothermia where the ability to rewarm is almost completely lost.

The process of arousal is apparently the same whether the awakening is evoked by an external stimulus or whether it occurs naturally during the hibernating cycle. One of the first signs of awakening is an increase

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in heart rate accompanied by a decrease in peripheral resistance. The exact sequence of events is difficult to trace, but respiratory rate and oxygen consumption rise before a detectable rise in body temperature. In the animals examined to date, the heart rate increases for several minutes before the blood pressure begins to rise (fig. 9). Once arousal is well under way, the rise in blood pressure is rapid and is accompanied by an ever-increasing metabolic rate. Shivering, which at first can only be determined electromyographically, soon becomes so gross that the whole anterior portion of the animal shakes with the effort.

It is characteristic of waking hibernators that the anterior of the animal warms rapidly, while the posterior remains near the temperature of deep hibernation (see fig. 9). This interesting economy of effort is caused by a circulatory control that appears to be an exaggeration of an ability found in non-hibernating mammals. The rat rewarming from hypothermia shows some of the same capabilities but not to such a refined extent. Injection of radiopaque material into the left ventricle of hamsters arousing from hibernation has demonstrated that circulation to the posterior part of the body is inhibited, and it is reasonable to assume that this is accomplished by differential vasoconstriction so that the circulation is mostly confined to the heart, lungs and brain (figs. 10* and 11). As arousal continues, the anterior portion of the body warms to nearly 37°C. before the rectal temperature changes markedly. The rectal temperature then rises rapidly and within a few minutes the body temperature of the whole animal has returned to the condition found during the normal active state. While the anterior part of the ground squirrel is warming, the mean aortic blood pressure continues to rise, but, once the posterior starts to warm, the blood pressure either drops or remains level (see fig. 9). It seems probable that the heart is able to develop and maintain a very high blood pressure when the blood flow is restricted but that, when the whole circulation is dilated, it cannot compensate for the decrease in total peripheral resistance. The importance of differential vasoconstriction during the warming process can be demonstrated by intra-arterial

*Figure 10 reproduced from Lyman and Chatfield: J. Exper. Zool. 114: 491, 1950. By permission of the Journal of Experimental Zoology.
injection of norepinephrine during the waking process. If such an injection is carried out while the rectal temperature is rising rapidly, the temperature ceases to rise for several minutes and the blood pressure increases. A series of such injections at intervals will cause the rectal temperature to rise in a stepwise fashion. 10

The arousal from hibernation involves a great metabolic effort and it has been calculated that as much energy is spent in one arousal as in 10 days of hibernation. Oxygen consumption rises rapidly as the anterior of the animal warms and reaches a peak at about the time the temperature of the anterior body attains 37 C. At the high point of metabolic effort, oxygen consumption is at least as great as in an active animal under conditions of maximum stress from exercise. The heart rate at the peak of metabolic effort is often 100 times as fast as the slow rate of hibernation. The whole animal seems geared to warm from its low body temperature in the least possible time, and the heart, beating at a rapid rate against a high head of pressure, may be an inefficient pump, but must contribute significantly as a heat source.

If one can generalize about the hibernating cycle by combining the observations on various species of hibernators, a fairly complete picture may be drawn. The animal in hibernation exerts a minimum metabolic effort conducive to life, deriving energy from stored fat, as evidenced by a respiratory quotient of 0.7. Vasconstriction maintains a livable mean blood pressure, and other homeostatic mechanisms function efficiently enough to permit existence. However, the hibernating animal is always poised for arousal and even as slight a stimulus as a quick puff of air can sometimes start the waking. Once started, arousal usually is carried to completion. In arousal, the decrease in peripheral resistance is caused by a vasodilation of the anterior portion of the body, while the posterior remains vasoconstricted. Shivering and respiratory movements contribute most of the heat to the waking process, though the totally curarized hamster can warm slowly from hibernation, presumably by using chemically engendered heat. 19 The main source of energy appears to be carbohydrate, for the glycogen of liver and muscle is greatly depleted during arousal. We have suggested that arousal is mediated and driven by a mass discharge from those somatic and sympathetic centers in the central nervous system that control temperature regulation in

Figure 11
Radiopaque material injected into heart of hamster waking from hibernation. X-ray taken 4 seconds after injection. Note lack of circulation to the posterior.
the active homeothermic mammal.\textsuperscript{20} Although subcortical electrical exploration of the brain of the waking hamster has failed to implicate the hypothalamus in the early part of arousal,\textsuperscript{21} there can be no question that the whole process is under precise control and that the autonomic system must play a part in this regulation.

The homeostasis that is typical of hibernation is maintained at body temperatures which are usually lethal to animals that cannot hibernate, and it seems to be typical of hibernators that their organ systems can function at very low temperatures. Thus the peripheral nerve of the Norway rat ceases to function at 9 to 10°C, while that of the hamster will conduct at temperatures as low as 2°C (fig. 12).\textsuperscript{22} The hearts of most animals that do not hibernate stop between 16 and 10°C, while the hearts of some animals that hibernate will continue an organized beat at -1°C. At slightly below this temperature, the blood itself would freeze. If the heart rate is plotted against temperature in the perfused, isolated heart of a nonhibernating mammal, the graph is nearly linear, and the temperature at which the heart will stop can be predicted with some accuracy by extrapolating the slope of the temperature-rate curve at high temperatures. Dawe and Morrison\textsuperscript{23} were the first to point out that this is not the case in animals that hibernate, for there is a break in the temperature-rate curve at about 15°C, and the hibernator’s heart continues to beat at lower temperatures than would be predicted. The hearts of nonhibernating species that are phylogenetically closely related to species that do hibernate show no particular resistance to cold, yet the hearts of all species of hibernators that have been tested to date are resistant to cold even though they may be only remotely related phylogenetically (fig. 13). This suggests that the ability to hibernate may have been developed separately among various species of mammals, and the ability to function at low temperatures is a result of the development of the hibernating habit.\textsuperscript{24} For those who consider hibernation a primitive characteristic, it is of some interest that the most primitive living rodent, the mountain beaver (\textit{Aplodontia}), possesses a heart that is as sensitive to low temperatures as one of the most phylogenetically advanced rodents, the Norway rat (see fig. 13).

\textbf{The Physiologic Thermostat}

If one grants that the hibernators as a group possess organs and tissues that function

\begin{figure}[h]
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\includegraphics[width=0.5\textwidth]{figure12.png}
\caption{Effect of temperature (C.) on the action potential of the isolated tibial nerve of hamster (left) and rat (right). (From Chatfield et al.\textsuperscript{24})}
\end{figure}

\textsuperscript{*}Figure 12 reproduced from Chatfield et al.: Am. J. Physiol. 155: 179, 1948. By permission of the American Journal of Physiology.
at temperatures lethal to nonhibernators, it is not hard to imagine that the hibernating mammal could keep in a steady state by reacting slowly, albeit effectively, to internal or external changes. The problem, however, is not simply one of cells and tissues that can function at unusually low temperatures. When exposed to extreme cold, an active hibernator resists chilling by pilo-erection, shivering, and the other methods of heat generation and conservation that are typical of mammals as a whole. If the cold is overpowering, body temperature drops and the hibernator enters a hypothemic state. In hypothermia, a hibernator will live longer, and at a lower temperature, than a mammal of the same size that is incapable of hibernation. However, it cannot rewarm from near-freezing temperatures without exogenous heat, and if left in hypothermia it will die within 24 hours.

We are thus left with the concept that hibernators have some way of turning down or resetting their “physiologic thermostat.” Because of this ability, they have a specialization of temperature control that is unique to them.

Figure 13
Effect of temperature on the rate of isolated hearts of hibernators (top four graphs) and non-hibernators (bottom four graphs). Closed circles = first cooling; open circles = rewarming. Triangles on graph of grey squirrel indicate ectopic ventricular beats only.
alone among the vast array of mammals as a Class. The “resetting” must involve changes in both the somatic and autonomic nervous systems, but the precise nature of these changes is largely a mystery. We know that the changes must be coordinated and that every change must be reversible, so that it is not likely that some sort of endogenous metabolic depressant plays a key role in the process. It may be that hibernation is an exaggerated form of sleep. If so, it is a big enough problem to keep us busy for some time.

References

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Alfred P. Fishman and CHARLES P. LYMAN

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