PHYSIOLOGY OF HIBERNATION AND RELATED LETHARGIC STATES IN MAMMALS AND BIRDS

by

PAUL RATHS (†) and ERWIN KULZER

DEDICATED TO PROF. DR. MARTIN EISENTRAUT IN CELEBRATION OF HIS 75TH BIRTHDAY

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Fig. 1: Hazel-mouse *(Muscardinus avellanarius)* — one of the smallest hibernators.

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Prof. Dr. Paul Raths

died in September 1976 from a tragic accident.

His German colleagues

lost an excellent physiologist

and naturalist.

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I. Introduction

Since the first comprehensive reviews on hibernation by Lyman and Chatfield (1955), Eisentraut (1956) and Herter (1956), many monographs and symposia have been published dealing with torpid states (Bligh 1973, Fisher et al. 1967 a, Hensel et al. 1973, Hoffmann 1964 b, Hudson and Bartholomew 1964, Hudson et al. 1972, Jansky and Musacchia 1974 a, Johansson and Senturia 1972 a, Kalabukov 1956, 1969, Kayser 1957, 1961, Lyman 1961, Lyman and Dawe 1960, Musacchia and Saunders 1969, Raths 1975, Shtark 1965, Slonim 1971, Smith et al. 1972, South et al. 1971, 1972 a, Suomalainen 1964, Swan 1974). Nevertheless, the problem of "lethargy" is far from being solved. The more important unsettled questions are concerned with biochemical functions and central nervous system controls.

The various lethargies can be subdevided into yearly or daily lethargies. To the former belong hibernation (Winterschlaf), aestivation (Sommerschlaf) and winter sleep (Winterruhe) of bears; to the latter belong the day and night sleep lethargies (Tages- und Nachtschlaf-Lethargie). The lowering of body temperature always takes place spontaneously, thus clearly distinguishing it from forced hypothermia (Kayser 1960). Arousal is always possible without external rewarming. A direct transition from aestivation to hibernation is possible (Kalabukov 1956) and in many respects these two lethargies are not distinguishable from each other (Bartholomew and Hudson 1960, Bartholomew and MacMillen 1961). There are also transitions from daily lethargy to hibernation (Eisentraut 1934, 1956, Kulzer et al. 1970, Scholl 1974). The close relationship between them is indicated also by their occurence in related animal species.

The term hibernation season is defined as the annual season in which the animals remain in hibernation. A series of days of uninterrupted torpor is called a "bout". It alternates with days of wakefulness. Hibernation and aestivation in poikilotherms and also artificial hypothermias which are in some cases similar to true torpor, for example magnesium-insulin hypothermia (Giaja 1940) and helium-hypothermia (Musacchia et al. 1971 b, Volkert and Musacchia 1970), are not disussed here in detail.

Distribution: Hibernation is found at least in 6 orders of mammals (Eisentraut 1956, Hensel et al. 1973, Herter 1956, Kayser 1961). Within a superfamily, family, genus or even within a species, one can frequently find different states of lethargy in close relatives. Of course, there are also related species without the capacity for torpor. A complete list would fill several pages. Therefore only the most important examples are given here.

Daily torpor and hibernation are described in the Monotremata (echidna) (Allison and Twyver 1972, Augee et al. 1970) and in several species of Marsupialia (Eisentraut 1956, Hensel et al. 1973, Kayser 1961, Raths 1975).

Fig. 2: Common dormouse *(Glis glis)* in natural hibernation. Note the ball-like position.

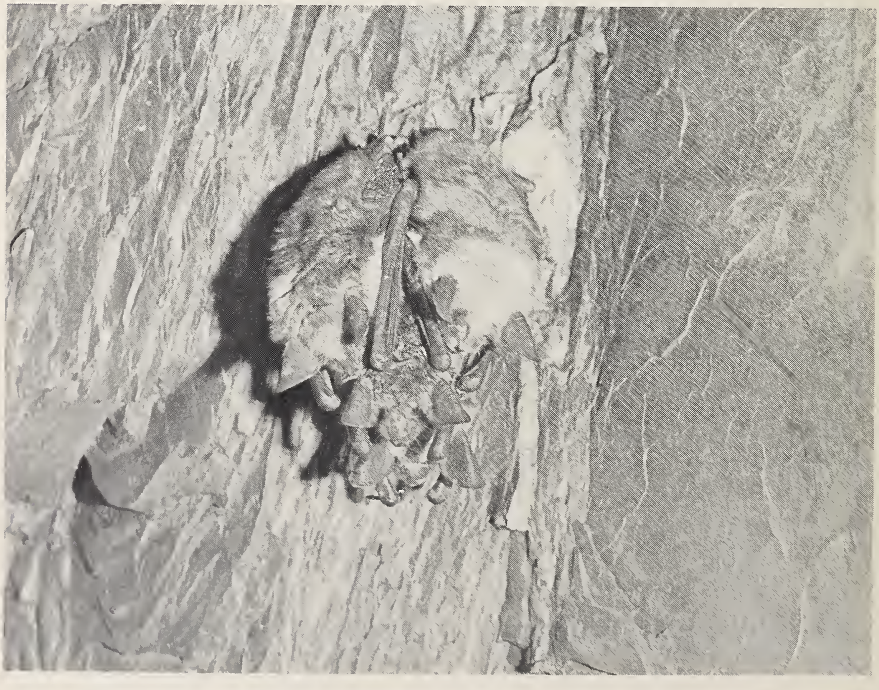

Fig. 3: A group of hibernating bats *(Myotis myotis)* in a cave.

Among the rodents, e. g. ground squirrels and marmots, all types of lethargy as well as the largest number of "sleeping" species can be found (Bartholomew and MacMillen 1961, Cade 1964, Hudson 1964 a, 1967, Hudson et al. 1972, Johansen and Krog 1959, MacMillen 1965, Morrison and Ryser 1962 a, 1962 b). Hibernation and/or daily lethargy occurs in bats (Chiroptera) (Eisentraut 1956); hibernation and/or aestivation in hedgehogs (Insectivora) (Herter 1964 a, b), hibernation or aestivation and daily torpor in tenrecs from Madagaskar (Eisentraut 1955, Herter 1962, 1964 a, Hildwein 1970, Hildwein and Kayser 1970, Scholl 1974). Bears were observed in winter sleep with body temperatures near 31°C. Skunks and racoons (Carnivora) probably do not enter a lethargic state (Folk et al. 1968). Torpor was also observed in several prosimians from Madagaskar (Eisensentraut 1956, 1961, Kayser 1961).

Fig. 4: The bat *Myotis myotis* in deep hibernation covered with water droplets (rel. humidity in the cave 95 %).

Daily periods of torpor have been found in several related bird families (Dawson and Hudson 1970), such as hummingbirds (Trochilidae), swifts (Apodidae) and nightjars (Caprimulgidae). Torpor was also described in different species of true swifts (Apodinae), in mousebirds (*Colius striatus),* Inca doves, turkey vultures, blackbirds (Lewies and Dyer 1969) and several other species. Spontaneous arousal is possible even at low ambient temperatures (Peiponen 1966). Nestlings enter the lethargic state more easy than adults (Dyer 1968, Koskimies 1948).

The distribution of lethargy in closely related species, genera and families indicates a **common phylogenetic** origin of torpor within the related forms. On the other hand, the existence of torpor in non-related orders indicates a **polyphyletic** evolution. Further, the absence of lethargy in closely related species argues against the interpretation of torpor as a primitive character, but suggests that it may be an adaptive "advance" in the evolution of temperature regulation, thereby allowing the species better to survive periods of fasting, to populate arid and hot regions (ground squirrels: Hudson 1969, Hudson et al. 1972; tenrecs: Kulzer and Koch 1976) and to migrate into temperate and cold climatic zones (bats: Kulzer 1965). Finally, this adaptation enables the very small species (hummingbirds, bats, birchmice) to survive during cool nights or cold periods by suppressing the enormous thermoregulatory requirements and so reducing the food requirements.

Fig. 5: The European hedgehog *(Erinaceus europaeus)* in its winter shelter.

As a consequence of the polyphyletic evolution of torpor, the various criteria of torpor may have different underlying biochemical mechanisms. This may lead to apparent contradictions. Further, body temperature, ambient temperature and the length of lethargic bouts play distinct roles, although, precise information on these is often absent in the literature. The same is true both for the prehibernatory thermal adaptation and for the time of the annual season. In the same species hibernation in January shows different physiological parameters from that in April.

Abreviations: T_a ambient temperature
T_b body temperature, core temperature
T_i incubation temperature

II. Mineral and Water Metabolism

To maintain nervous excitability and efficiency of organs during torpor, the intra- and extracellular **ionic conditions** must be maintained or certain adaptive re-adjustments of mineral and water metabolism must take place (Fisher and Manery 1967, Willis et al. 1972).

Sodium and Potassium: Isolated tissues from heart (with the exception of *Peromyscus,* Hudson and Eller 1974), diaphragm (Willis 1962), neocortex, brainstem (Bowler and Duncan 1969, Saarikoski 1968, 1969, 1970 a, 1970 b), kidney (Bidet et al. 1965) and erythrocytes (Kimzey and Willis 1971 a, 1971 b) from awake hibernators have a substantially greater resistance to cold swelling (Na^+ and H_2O-influx and loss of K^+) than have rats and guinea-pigs. Further, the disposition to hibernate, and the torporous state itself, raise the resistance of tissue (Fang 1971, Willis 1968, Willis et al. 1971). In this decrease in sensitivity to cold, the Na-K-ATPase plays a definite role. On the other hand, several enzymes of kidney tissue (acetylcholinesterase, acid and alkaline phosphatase, NADH-diaphorase) do not adapt (Fang 1971, Willis 1966, 1967, Willis et al. 1972). Willis suggests that the greater effectiveness of the Na-K-pump in hibernators is related to a direct coupling between oxydation and the transport of ions.

Investigations in situ in hibernators to some extent show different results from above. **Artificial hypothermia** leads to a tissue swelling (Brendel et al. 1966, Raths 1962) and to a rise in permeability of the blood-brain barrier (Wells 1972). An interpretation of the hibernation syndrome is very difficult owing to this disagreement. The Na-concentration in plasma and serum shows no definite changes during torpor (Denyes and Hassett 1960, Edwards and Munday 1974, Hoo-Paris and Garcin 1970, Moy 1971, Nelson et al. 1973, Pengelley et al. 1971, Raths 1964, Soivio and Kristoffersson 1974). In only a few cases was a rise observed (Ambid 1975, Clausen and Storesund 1971, Raths 1962, Zatzman and South 1972).

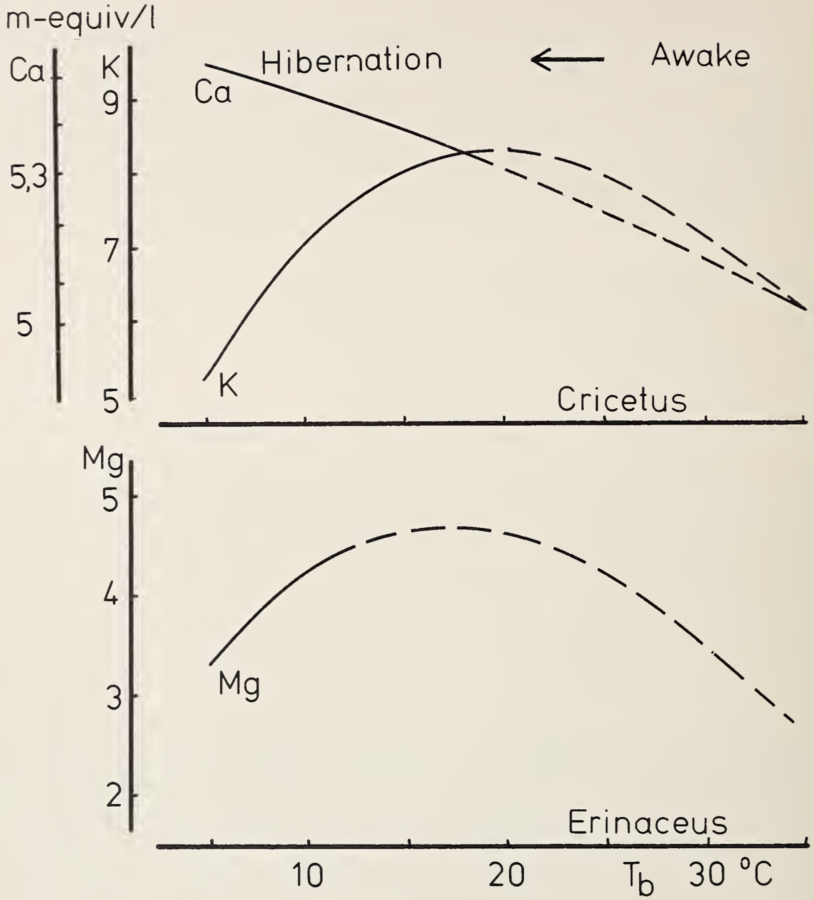

Fig. 6: Serum calcium and potassium concentrations at various body temperatures in the European hamster. Below, plasma magnesium concentration in the hedgehog (average curves). From Raths (1962), Edwards and Munday (1974).

During hibernation, the Na-concentration of different tissues either shows no changes at all (Clausen and Storesund 1971, Vysochina 1971, Willis et al. 1971) or a decrease. Unfortunately it is not exactly known at what T_b and under which conditions, even in hibernation, can a Na-inflow take place. Generally, these findings argue for the functioning of the Na-pump during hibernation. It seems that there is no dependence on T_b.

The **K-concentration** in the blood during hibernation can be unchanged (Moy 1971, Nelson et al. 1973, Pengelley et al. 1971, Riedesel 1960, Zatzman and South 1972) or increased (Clausen and Storesund 1971, Eliassen 1963, Hoo-Paris and Carcin 1970, Tempel and Musacchia 1975) or decreased

(Ferdmann and Feinschmidt 1934, Riedesel 1960, Soivio and Kristoffersson 1974). It is possible that immediately after the "switch over" from the awake state to hibernation, a common poikilostatic phase with a K-rise takes place. As soon as T_b is lowered (17°—12° C) the K-concentration will be readjusted to its normal level (Raths 1962, 1964, Edwards and Munday 1974).

The tissue K-concentration in heart, muscle, brain, liver and the cortical zone of the kidney during hibernation is unchanged or even increased (Clausen and Storesund 1971, Tempel and Musacchia 1975, Vysochina 1971). But not all tissues act in the same way: muscle, skin and erythrocytes may lose K (Andrus et al. 1965, Vysochina 1971, Willis et al. 1971). Probably several tissues, especially in the kidney, take up ions passed out of other tissues. After arousal, the K-concentration in the blood and the cells is again normal (Kimzey and Willis 1971 a, Raths 1962, Willis et al. 1971). Raised blood K-values may be caused by K-exit from muscles during shivering.

Magnesium: In artificial hypothermia, Mg-ions like K-ions leave the cells and enter the blood (Mendler et al. 1972 a). In hibernation also a strong rise of the Mg-concentration in the blood was observed in many species (Clausen and Storesund 1971, Raths 1964, Soivio and Kristoffersson 1974). In a few cases, the level remained constant or was even lowered (Edwards and Munday 1974, Raths 1964). The Mg-rise has been implicated as a major factor in the initiation of hibernation (Riedesel 1960, Suomalainen 1939).

But the elevated serum magnesium is not only a characteristic of hibernation per se, but it is also found in homeotherms during hypothermia and cold acclimatization (Pengelley and Chaffee 1966, Suomalainen et al. 1969). The magnesium level may even return to normal at very low T_b (Edwards and Munday 1974). Finally Pengelley et al. (1971) found by aortic cannulation which makes it possible to sample blood of a hibernating animal *(Citellus lateralis)* in a way that does not cause arousal, that the concentrations of all plasma electrolytes remain constant even during long periods of torpor until the next arousal.

Calcium: During hibernation, bones and teeth loose Ca (Bruce and Wiebers 1970, Ferren et al. 1971, Mayer, W. V. 1960, Kayser et al. 1964) which is deposited in skin, liver, muscles, fat, heart and brain. The loss of mineral from bone is also reflected by an increased loss of phosphate in the urine during the hibernation period. Simultaneously, the Ca-level in blood increases (Ferdmann and Feinschmidt 1934, Hoo-Paris and Garcin 1970, Raths 1962, 1964, Soivio and Kristoffersson 1974). In some cases, blood-Ca either remained constant or fell (Kayser 1961, Raths 1962, Riedesel 1960). The Ca-mobilization during hibernation can be explained as an increased function of the parathyroid gland (stimulating osteoclastic activity) and the lowered activity of the C-cells.

Water compartments: In hibernating bats under normal environmental conditions, the total body water content either does not change or increases a little (Kallen 1964, Krulin and Sealander 1972). The ability to hibernate is lost after water deprivation or dehydration (Kallen 1964, Pirlot 1968). In all the smaller hibernating species, there is the danger of dehydration during torpor (Kayser 1961). Lack of water may be an important cue for lethargy and aestivation (Bintz et al. 1971, Isaakjan and Felberbaum 1954, MacMillen 1965), especially in those species which have no resistance against water loss (Riedesel 1960). Many investigators give their experimental animals only dry food, to accelerate onset of hibernation.

It is quite certain that during hibernation there are water movements between the different body compartments and between the organs. For example, the intracellular space shrinks in the hibernating golden hamster and in the thirteen-lined ground squirrel (Folk and Farrand 1957), while it increases in the hedgehog (Clausen and Storesund 1971). In many cases, uptake of water occurs in the liver (Kayser 1961, Kristoffersson et al. 1965) while muscles lose water (Clausen and Storesund 1971, Eliassen and Egsbaek 1963, Kristoffersson et al. 1965). The findings in other organs are very contradictory (Belskaya and Khachatryan 1971, Luyet 1964, Platner et al. 1972, Willis 1962). All results indicating hemoconcentration — for example, the increase of specific weight (Hock 1964), protein content, hematocrit (Eliassen and Egsbaek 1963), RBC, Hb-values, and viscosity (Nelson et al. 1973) must not be interpreted unconditionally to indicate dehydration of the blood. Changes in protein metabolism, erythropoiesis, and the conditions of circulation come into play. Frequently, hemodilution during torpor was described (Hock 1964, Riedesel 1960).

The dehydration of the body is prevented by suppression of urine formation during hibernation. Further, in the "winter-sleeping" black bear (Nelson et al. 1973), and possibly in the hibernating marmot (Zatzman and South 1975) a water reabsorption from the bladder is discussed. In the ground squirrel *(Citellus erythrogenys)*, protection against dehydration by an increase in hyaluronidase activity in the intestine is supposed by Belskaya and Khachatryan (1971).

Kidney function: During hibernation and during winter sleep, micturition does not take place (Folk 1967), though during the prehibernatory phase, the kidney weight as well as mitotic activity, DNA- and N-content and activity of oxydizing enzymes increase (Denyes and Hassett 1960, Senturia and Johansson 1972), so that theoretically the production of urine seems possible. Published results show that relative to the level under normothermic conditions the urine production is strongly reduced to 3 %—20 % in the lethargic hedgehog (Clausen 1964), 10 % in the thirteen-lined ground squirrel (Hong 1957) and the marmot (Zatzman and South 1975), 1 % in bats (Kallen and Kanthor 1967) and 5 % in the bear (Nelson et al. 1973). Hibernation leads to a decrease in the glomerular filtration rate, with a greater fall in plasma flow than filtration rate. The filtration fraction may be almost doubled. This is the result of an increase in renal vascular resistance during torpor (Brown et al. 1971, Zatzman and South 1972). Surprisingly in marmots inulin clearance decreases until the 5th or 6th day of torpor (Zatzman and South 1975). Histological studies and investigations on urine composition in different species have supported these results (Amon et al. 1965, Herzog 1964, Petry et al. 1964, Zimny and Levy 1971).

During hibernation, the activity of the antidiuretic hormone is reduced. The counter-current system therefore is inefficient (Lesser et al. 1970, Moy et al. 1972) and the urine is diluted (Clausen 1964, Clausen and Storesund 1971, Eliassen 1963, Ferdmann and Feinschmidt 1934, Kristoffersson 1965, Tempel and Musacchia 1975), exceptionally so in marmots, bears and golden hamsters (Zatzman and South 1975, Brown et al. 1971, Denyes and Hassett 1960). The excretion of Mg, Ca and phosphate is markedly increased (Bruce and Wiebers 1970, Kayser and Haug 1968), probably as a result of the increased concentration in the blood. In contrast, the excretion of acids and ammonia is reduced during torpor (Ferdmann and Feinschmidt 1934, Hong 1957). The hibernation-acidosis therefore is not counterbalanced by the kidney, but is probably "intended" by the animal.

A change in tubular function may be inferred from the absence of Mg-ATPase and the increase of Ca-ATPase in the basal lamella as well as from the higher activity of Mg-ATPase in the tubular Golgi-zones (Rosenbaum and Melman 1964). The increase in K-excretion, as compared to Na (Eliassen 1963) is probably correlated with a decrease in cold sensitivity of the Na-K-ATPase. It is also worth mentioning that the juxtaglomerular apparatus shows an increased secretion of renin (Brown et al. 1971, Slonim 1971, Zimny and Levy 1971). That is accompanied by histological changes indicating activation of the zona glomerulosa of the adrenal gland during hibernation.

During the arousal process, urine production ceases totally for a while as a consequence of abdominal vasoconstriction (Lesser et al. 1970, Moy et al. 1972) but between T_b of 23—31° C — after removal of the constriction — urine production returns to normal (Moy 1971). Thereby the counter-current system becomes effective again.

Summary: In spite of the decreased kidney function, during hibernation adaptive and regulatory changes in enzymes and stabilization of mineral and water metabolism take place. These factors maintain a constant level of serum-Na, and account for a return of serum-K to normal after an initial increase, and for an increase of serum-Ca and -Mg.

III. Heart and Circulation

Electrophysiology of the heart: Several comprehensive articles and reviews on electrical changes in the heart of hibernators have been published (Dawe and Landau 1960, Johansson 1967, Lyman 1965, Nardone 1955, Sarajas 1954). In contrast to other mammals, the excitability and the membrane resting and action potentials from heart tissue of hibernators can be influenced only a little by low temperatures (Marshall and Willis 1962). Hibernation raises the resistance against cold even further (Jacobs and South 1976). Resistance against lowering of pH (Souhrada and Bullard 1971) and against ventricular fibrillation (Johansson 1963) appear to be additional distinctive features of the hibernating heart.

The peculiarities of the ECG consist of a very short ST-segment (Johansson 1967) and a relatively small temperature dependence for the time of repolarization. Often reported are a notched R-wave, a left bundle branch block and an atrioventricular dissociation, even in lethargic hummingbirds (Lasiewski 1964). However these changes are probably signs of the beginning of arousal (Lyman 1965).

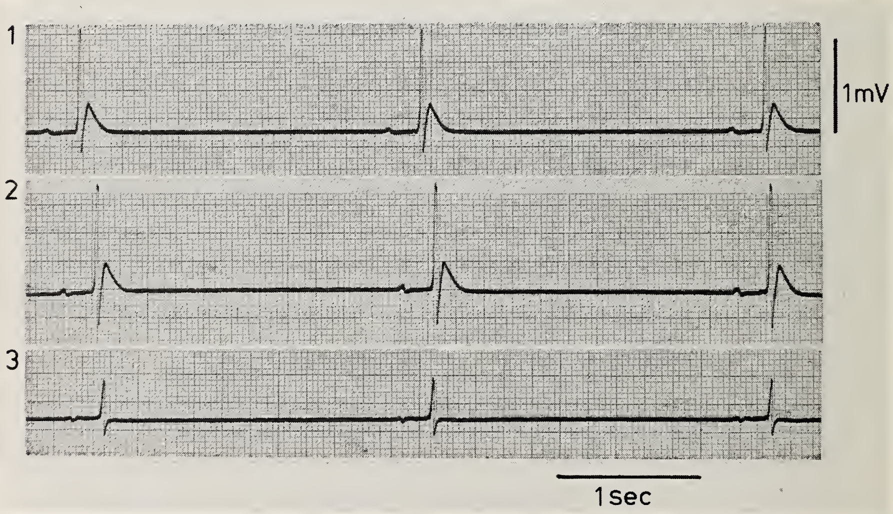

Fig. 7: *Myotis myotis* ECG during deep hibernation; T_b 8,7° C, lead I, II, III (Kulzer 1967).

Mechanical properties of the heart: A comparison of heartmuscle strips from non-hibernating and hibernating mammals show that the tension production is less temperature dependent in hibernators, probably as a consequence of the special characteristics of the "active state" (defined as the force which can be developed by the contractile element remaining at a constant length). Likewise, the strength of the cardiac contraction of an electrically driven heart is larger in hibernators (Alpert et al. 1972, Hudson and Eller 1974, Smith and Katzung 1966, South and Jacobs 1973). In the lethargic marmot, there is a reciprocal relation between T_b and stroke volume. In spite of this, the cardiac output during hibernation drops as a result of the decreasing frequency to one tenth of the normal value (South and Jacobs 1973). Certainly, the rise of the stroke volume plays a role in preventing an extreme drop in blood pressure. The "grouped beats" in hibernating marmots can be interpreted in the same way. They probably originate as oscillatory "reverberations" of each first real cardiac contraction (Armour et al. 1974). This may be the result of a rise in the sympathetic tone and an increase of blood-Ca during lowering of T_b. A Ca-influx into the cardiac muscle celles along the transverse tubules may be possible even in hibernation.

Heart rate: Isolated hearts from hibernators cease to beat between −5° and +7° C (Hudson 1971, Hudson and Eller 1974, Lyman 1965). In a narcotized bear the heart stopped at 16° C after ventricular fibrillation (Folk et al. 1965). Heart rate/temperature curves in isolated hearts (Hudson 1971, Senturia et al. 1970) and isolated cardiac muscle cells (Andrus 1969, Lyman and Jarrow 1971) of hibernating mammals have been derived several times. Only in few cases do these curves fit the Arrhenius equation over the whole temperature range. Also, the decrease in activation energy during hibernation not always occurs.

The sympathetic tone drops before the onset of hibernation, while the vagal tone is increased. Therefore in autumn, the mean heart rate of the normothermic ground squirrel decreases and the heart of the hedgehog becomes arrhythmic. Although dominated by the parasympathetic component, fluctuations in tone of the autonomic nervous system become extremly high during the onset of the diurnal lethargy and hibernation (Kulzer 1967, Lyman 1965). Therefore, during decreasing T_b and decreasing mean heart rate, phases of brady- and tachycardia alternate, and the so-called "step phenomenon" appears (Lyman 1965, Lyman and O'Brien 1964, Morhardt 1970, Strumwasser 1960) and ventricular force changes frequently (Armour et al. 1974). However, the vagal nerve loses its effectiveness between T_b of 9°—12° C (Biewald and Raths 1959, Biewald 1974). In isolated hearts the negative chronotropic response to acetylcholine is lost at 10° C T_i (the negative inotropic response is already lost below 20° C T_i) (Turpayev 1948). It is certain that the blockage of the vagal inhibitory effect is not caused by the loss of nerve conduction or the loss of excitability, but perhaps by a disturbance of the coupling mechanism (Biewald 1967 a, Biewald and Raths 1967). With respect to the increased serum-Ca during hibernation, it should be mentioned that the vagal mechanism of the isolated rabbit heart becomes ineffective as a result of an elevation of the external Ca (Nilius 1973). In agreement with this hypothesis is the fact that the activity of the cholinesterase in the hibernating heart and in other tissues is, in general, not

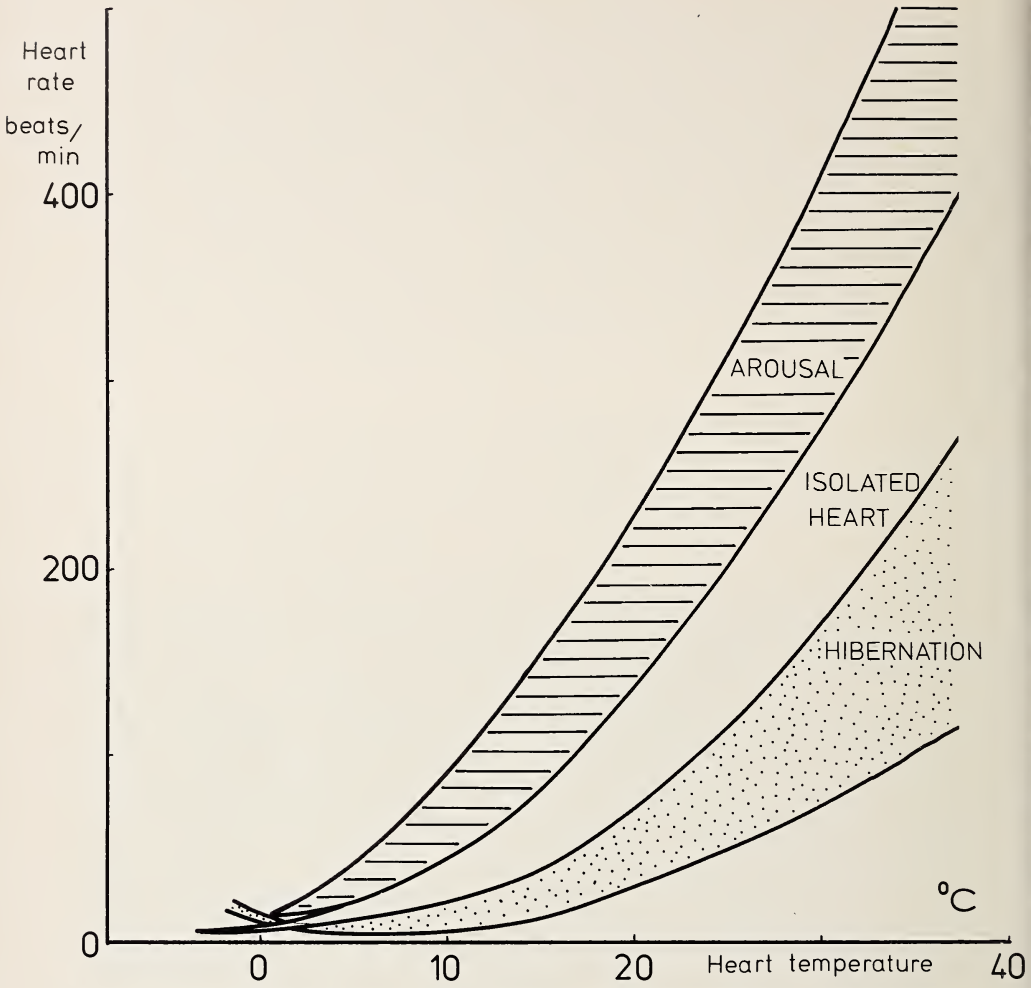

Fig. 8: General dependence of heart rate on the heart temperature in hibernators including following species: *Citellus tridecemlineatus, C. tereticaudus, C. mohavensis, C. mexicanus, C. beecheyi, Tamias striatus, Marmota monax, Mesocricetus auratus, Cricetus cricetus, Myotis myotis, M. lucifugus, Erinaceus europaeus* (adapted from many authors).

diminished (Lyman and O'Brien 1969, Zimny 1964) and its temperature dependence is amazingly low.

All authors agree that during hibernation there is not a strong correlation between T_b and heart rate (Kayser 1961, Kristoffersson and Soivio 1964, Kulzer 1967, Lasiewski 1964, Nardone 1955). If the vagal nerve is blocked, changes in heart rate and force, in spite of a constant T_b, can only be the

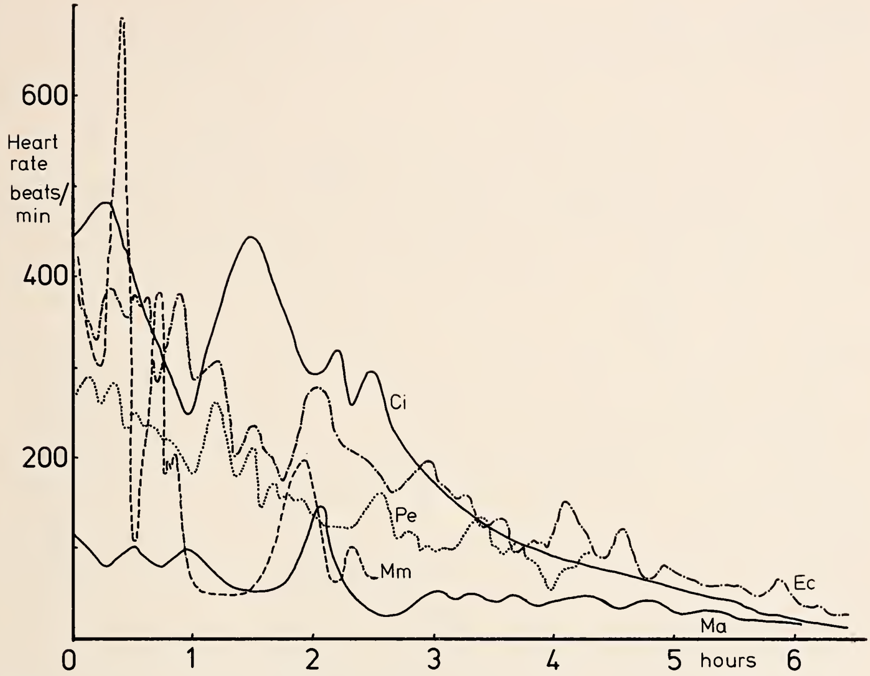

Fig. 9: Heart rate during entrance into torpor. Ma = *Marmota monax*, hibern., T_a5° C (Lyman 1958), Ci = *Citellus tridecemlineatus*, hibern., T_a 5° C (Lyman and O'Brien 1960), Pe = *Perognathus hispidus*, daily torpor, T_a 11° C (Wang and Hudson 1970), Ec = *Echinops telfairi*, daily torpor, T_a 20° C (Scholl 1974), Mm = *Myotis myotis*, hibern., T_a 10° C (Kulzer 1967).

result of sympathetic (regulative) influences. In an extreme case during cold stress in hibernation, a negative correlation between T_b and heart rate may emerge (Davis 1970, Kayser 1961). Thus a reflex acceleration of heart rate during hibernation is possible (Armour et al. 1974, Kristoffersson and Soivio 1964, Lyman 1965). The isolated heart of *Citellus* reacts to adrenaline even at a T_i of 4° C with a very strong positive inotropic effect (Turpayev 1948). Arousal from hibernation and from daily lethargy leads to a powerful sympathetic activation of the heart (Lyman 1965, Morhardt 1970), so that at first cardiac output and later heart rate increase (Kirkebö 1968). In species with very small body weight, extremly high heart rates were recorded (Bullard 1964, Kulzer 1967, Lasiewski et al. 1967, Rauch 1973).

Microanatomy of the heart: It is possible that some special properties of the hibernating heart depend on special structures within the cells. Such differences — in comparison to normothermic conditions — may result in a tighter integration at the structural level, by storage of granules and by an enlargement of the Golgi apparatus (Poche 1959, Rosenqvist 1970). This

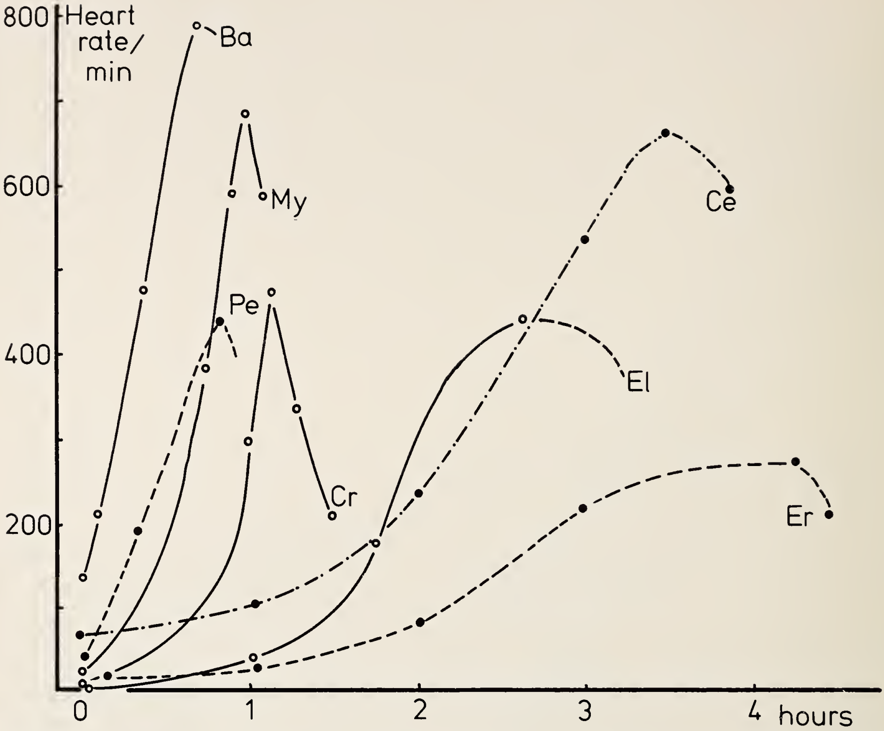

Fig. 10: Heart rate during arousal from torpor. Ba = *Baiomys taylori,* daily torpor (Hudson 1965), My = *Myotis myotis,* hibern. (Mejsnar and Jansky 1970), Pe = *Peromyscus hispidus,* daily torpor (Wang and Hudson 1970), Cr = *Cricetus cricetus* (Raths, not publ.), Ce = *Cercaertus nanus,* hibern. (Bartholomew and Hudson 1962), El = *Eliomys quercinus,* hibern. (Pajunen 1970), Er = *Erinaceus europaeus,* hibern. (Kirkebö 1968).

could result in a better Ca-absorption by the cells with the already mentioned consequences. According to other authors, however, such differences do not exist (Aloia and Pengelley 1971, Belov and Semenova 1971) or if they do, they are the result of degeneration of the tissues.

During torpor and in the normothermic state, the adrenergic innervation of the heart, as well as the concentration of noradrenaline, correspond to normal mammalian standards (Angelakos et al. 1971, Lew and Quay 1973). But the sympathetic innervation of the cardiac vascular system may be more dense, to the disadvantage of the muscle cells (Nielsen and Owman 1968). Further studies on enzyme activity have shown seasonal variations in the formation and the concentration of noradrenaline in the hedgehog heart (Johansson and Senturia 1972 a), which are in agreement with the diminished turnover rates in winter (Draskoczy and Lyman 1967). However, such alterations probably are not responsible for the lethargic heart function, since, especially in the hedgehog, an artificial insulin- or magnesium-hypothermia can be maintained several days without heart failure (Kayser 1961).

Peripheral circulation. During onset of hibernation, the vessels of the skin dilate (Chew et al. 1967, Strumwasser 1959 a), but in general, a uniform distribution of blood in the organism is maintained. Only the heart and the brown adipose tissue receive more blood per unit body weight (Bullard 1964, Soivio 1967, Wells 1971). At very low T_b, these two organs are probably of thermoregulatory importance. Owing to the decreasing heart rate, the dilation of blood vessels and of the storage of blood in the spleen (Elgjo and Eliassen 1963, Kallen 1960, Popovic 1964, Spurrier and Dawe 1973) and in the large veins (Eliassen and Egsbaek 1963), the blood pressure in the aorta drops to a systolic of 40—90 torr and a diastolic of 7—40 torr (Kirkebö 1968, Lyman 1965). During deep hibernation, the vascular tone is regulated by the sympathetic system (Lyman 1965, Strumwasser 1959 b), so that, on the whole, the tone increases and no extreme lethal drop of pressure occurs (Lyman and O'Brien 1963, 1964). Further influences on blood pressure arise from the altered extensibility of the large vessels (Kirkebö 1968) and from the alterations of blood viscosity (Halikas and Bowers 1973, Spurrier and Dawe 1973).

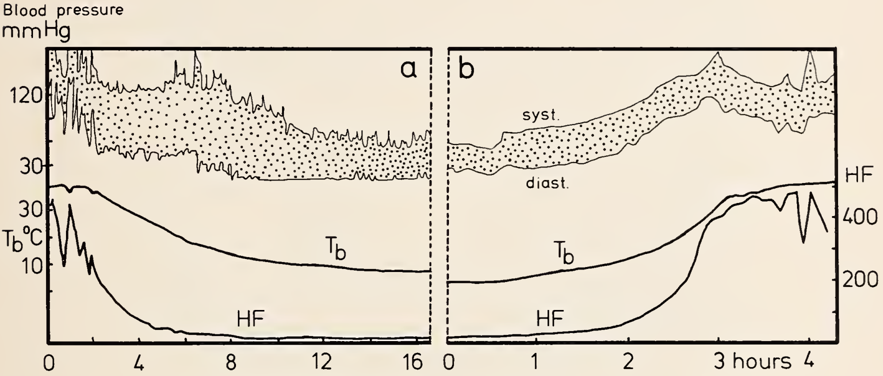

Fig. 11: Change in the aortic blood pressure, T_b and heart rate during entrance into hibernation (a) and arousal (b) in *Citellus tridecemlineatus*. Adapted from Lyman and O'Brien (1960). HF = heart rate (beats/min), T_b = heart temperature.

During arousal from hibernation, the blood flow decreases in the skin, in many skeletal muscles, in the posterior viscera, in the tail and in the tongue (Bullard 1964, Lyman 1965, Soivio 1967, Wells 1971), so that the thermal conductance decreases (Chew et al. 1967). Simultaneously, the blood flow rises in the brown fat, the myocardium, the thyroid gland and in various muscles of the anterior body (Johansen 1961, Rauch 1973, Soivio 1967, Wells 1971), so that rewarming of the brain and the thoracic viscera is accelerated. During arousal from aestivation, this redistribution of blood may be absent (Bartholomew and Hudson 1960). The restricted flow of peripheral blood is certainly the result of a sympathetic vasoconstriction (β-receptor excitation) (Kirkebö 1968, Lyman 1965). However, it is not evident why the vasoconstriction suddenly ceases at a head temperature of about 30° C, and why it can only be re-established for short periods by noradrenaline (Lyman 1965, Lyman and O'Brien 1963). At the beginning of arousal, the aortic pressure and the peripheral resistance drop for about 10—20 minutes (Kirkebö 1968), probably as a result of vascular dilation in several organs. Probably for the same reason, an increase in blood pressure appears more slowly than an acceleration of heart rate, in spite of a mobilization of additional blood from storage sites (Soivio 1967).

Summary: There are several hypotheses to account for the special properties of the hibernating heart, but no conclusive theory. During entrance into lethargy, the heart is controlled by the vagal-sympathetic system. During deep hibernation control is exclusively by the sympathetic component. Control of the peripheral circulation during deep hibernation and arousal is maintained by sympathetic activity.

IV. Nutrition and Digestion

Amount of food and body weight: Hoarding of food, hyperphagia and storage of fat are typical indicators of the preparation for hibernation. From their behaviour, one can distinguish "obligate" hibernators (for example *Perognathus*) and "seasonal" hibernators (for example *Citellus*). These two groups, with little or no food storage, contrast with the "permissive" hibernators (for example *Cricetus*), which store food on a large scale (Hoffman 1964 b). Bats neither show real hyperphagia, nor store food, but become very fat (Ewing et al. 1970). During the hibernation season, even in the awake state, the food intake is very small, so that in all species there is a large decrease (about 30%) in body weight (Kayser 1961, Kristoffersson and Suomalainen 1964, Mletzko and Raths 1972 a, Morrison 1960, Pengelley and Chaffee 1966, Senturia and Johansson 1972).

In hibernators, the hypothalamus is involved in the regulation of food intake (Mrosovsky 1971, 1974 a, b, 1975, Raths and Bohn 1975, Satinoff 1970). Mrosovsky has developed a hypothesis about a seasonal fluctuation in the hypothalamic set-point for appetite. This set-point may determine the onset of hibernation and the duration of hibernation bouts (Barnes and Mrosovsky 1974, Strumwasser 1959 a, 1959 b). Indeed body weight and the

Fig. 12: The hazel-mouse *Muscardinus avellanarius* during first month of hibernating period. The animal has nearly doubled its body weight preparing the hibernation.

disposition to hibernate are correlated and their phase is seasonally adjusted (Heller and Poulson 1970, Kayser 1961). The theory is supported by the fact that hibernation is stimulated by the prehibernatory storage of fat (Mrosovsky 1971, Satinoff 1970), and contradicted by the observations that the yearly rhythm of hibernation is not changed by food deprivation (Pengelley and Asmundson 1972), that thin animals also hibernate, and that food deprivation and even starvation stimulate hibernation (Kayser 1961, MacMillen 1965).

Generally, these contradictions are only apparent. Food deprivation stimulates hibernation only during the phase of hypophagia, while during hyperphagia (phase of storage) it disturbs hibernation (Graves 1971), so that no torpor can develop (Raths and Bohn 1975). In a similar way the motor activity may either be increased or decreased by food deprivation (Cornish and Mrosovsky 1966). Obviously hibernation is always supported by that food supply, which is correlated with the actual food requirements of the

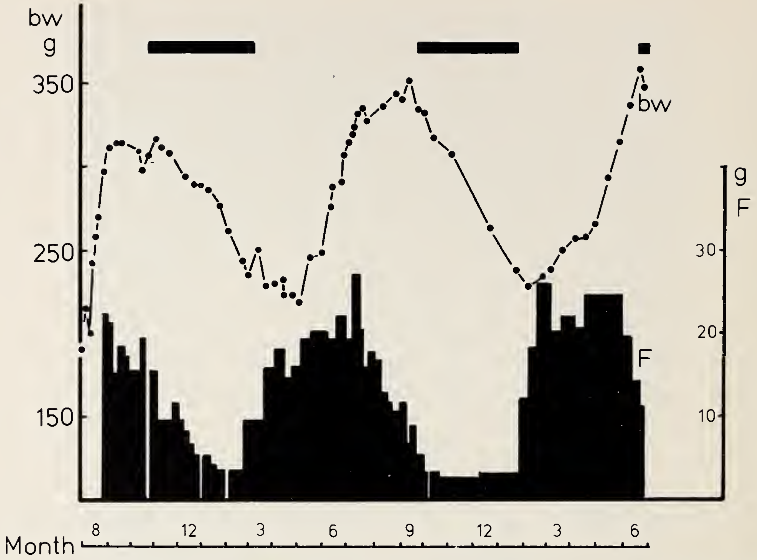

Fig. 13: Body weight (bw), mean daily food consumption in g (F) and hibernating periods (solid horizontal bars) of an individual *Citellus lateralis* observed for two years at T_a 22° C and LD 12 : 12. Adapted from Pengelley and Fisher (1963).

animal (Mrosovsky 1974, Raths and Bohn 1975). In many species, the annual rhythm of body weight does not depend on food supply, gonadal function (Canguilhem 1974), T_a and light conditions. The increase in body weight may be endogenously programmed. However, under constant light and temperature conditions the rhythm can be lost after 1—2 years (Mrosovsky 1971), so external signals may influence it. In some species it is influenced by the conditions of thermal adaptation (Mletzko and Raths 1972 a), the T_b during torpor, the frequency of arousal (Lachiver and Boulouard 1965) and the endocrine glands (Canguilhem and Malan 1969). There is agreement that food deprivation is one of the most important releasers of lethargy in birds and mammals (Bartholomew and Trost 1970, Dawson and Hudson 1970, Koskimies 1948, Lasiewski 1963, MacMillen and Trost 1967 b, Peiponen 1965, 1966).

Qualitative changes in nutrition: During summer, the captive dormouse prefers different food from that in autumn (Haberey et al. 1967, 1974). During summer and autumn, an increase in quantity and a change in quality of food produce, in various organs, an intense deposition of vitamins such as ascorbic acid (C), thiamine (B_1), riboflavin (B_2), vitamin A and tocopherol (E) (Kalabukhov 1956, 1969, Suomalainen and Ahlström 1970). During winter, these reserves are partially consumed. The known connection between vitamins and enzymes leads to the supposition that the storage of vitamins has something to do with enzyme alterations during hibernation.

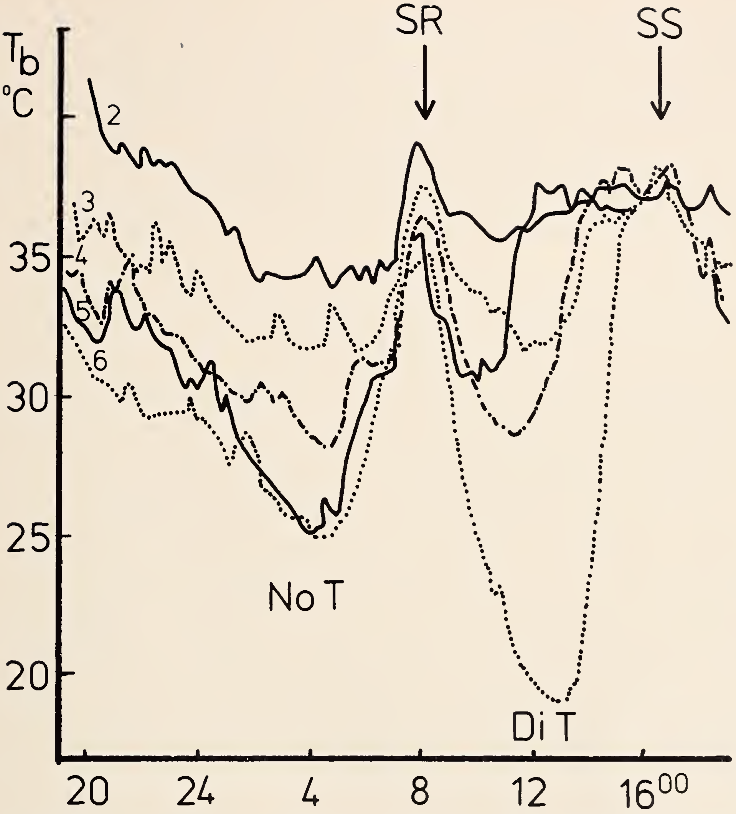

Fig. 14: Daily T_b- curves of a nightjar *(Caprimulgus europaeus)* during 5 consecutive fast days (No 2—6) in November. SR = sunrise, SS = sunset, No T = nocturnal torpor, Di T = diurnal torpor. Adapted from Peiponen (1965).

For example, an injection of tocopherol stimulates the disposition for lethargy (Kalabukhov 1969).

Digestive system: The diminished food requirements during winter are reflected by the extensive manifestations of inactivity in the digestive tract during hibernation. In histological and biochemical studies, an involution of salivary, intestinal and gastric glands can be observed (Henriksen 1972, Mayer W. V. 1960, Musil and Kittel 1968, Sacchi 1973, Sauerbier 1976, Slonim 1971). Further, there is a weight loss of the intestine and of the pancreas as well as a diminished protein content (Senturia and Johansson 1972). Arousal leads to a reactivation of the digestive system.

Summary: The instinctive habits of nutrition show quantitative and qualitative adaptations to the prehibernatory and hibernatory requirements of the organism, including the hibernation inactivity of the digestive tract.

V. Respiration and Blood Gases

Ventilation: Several adaptations appear during hibernation. The temperature-dependence of diaphragm contraction is diminished (South 1961) but the sensitivity of the diaphragm to acetylcholine (Moravec et al. 1973) and the Na-permeability of the subsynaptic membranes of phrenic endplates are increased (Melichar 1973). These adaptations, in spite of a simultaneous inhibition of the breathing center, may facilitate the ventilation of the lungs.

As is well known, the respiratory frequency during hibernation is not only very low but also very irregular (Eisentraut 1956, Herter 1956, Kayser 1961, Pajunen 1974). While periodical respiration is not absolutely typical for hibernation, it was frequently observed during daily lethargy, during onset of hibernation (Malan et al. 1973) as well as in deep torpor (Hoo-Paris and Garcin 1970, Kayser 1961, Kristoffersson and Soivio 1964, Pajunen 1970, 1974, Pirlot 1968), suggesting a diminished excitability of the respiratory centre. This was confirmed by a rise of the threshold for excitation of respiratory neurons by CO_2 (2.5 %—5.0 %) (Leitner and Malan 1973, Malan et al. 1973). In this connection, the concentrations for respiratory gases in the winter dens are of interest (Baudinette 1974, Williams and Rausch 1973). In different species, the values of CO_2 are usually below 4 %, and the values of O_2 above 13 %. Some abnormal values in marmots (13.5 % CO_2 and 4.8 % O_2) are understandable only as a result of an extremely strong inhibition of the respiratory centre. However, this could significantly shift the oxygen dissociation curve of the blood to the right at low T_b (Williams and Rausch 1973). Further, there are indications that even in normothermic hibernators (echidna, marmot) hypoxia and hypercapnia stimulate the respiratory neurons only slightly (Leitner and Malan 1973). On the other hand, the inhibitory effect of CO_2 on the heart of normothermic kangaroo rats is between the values of nonhibernators and some diving mammals. Because of such peculiarities the old theory of inducing torpor by hypercapnia was reconsidered by Malan et al. (1973) and Williams and Rausch (1973).

Carbon dioxide and blood pH: During the cooling of poikilotherms or hibernators, the CO_2-concentration in the blood rises as a consequence of the increased solubility of gases (Clausen and Ersland 1968, Kayser 1961), but simultaneously in poikilothermic vertebrates the arterial P_{CO_2} decreases (Howell et al. 1970). However, since the physical neutral point (pN) of water rises during cooling, so the measured pH must rise if the constancy of the H^+/OH^- relation is "maintained". That means, the lower the temperature of neutral water (or serum), the higher is the pH. Indeed the arterial pH in cooled poikilotherms increases parallel to the shift of the neutral point. Therefore, in spite of an increasing pH no alkalosis results, as the acid/base balance is kept unchanged (Howell et al. 1970). This must be kept

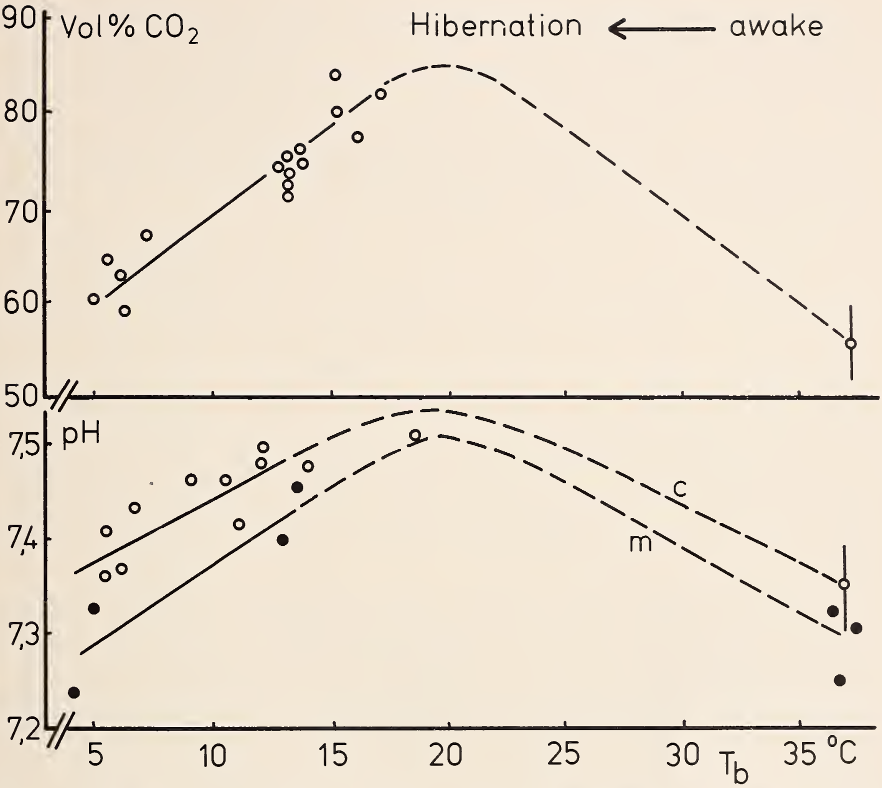

Fig. 15: CO_2-content of arterial blood in the spotted ground squirrel *(Citellus suslicus)* at different body temperatures, measured at T_i 18° C. Below, arterial blood pH, measured at different body temperatures (m) and calculated (c) from Person (1952).

in mind in order to understand the behaviour of hibernators. Nearly all data on blood pH and blood CO_2 during torpor were collected at very low T_b. We know of only one observation where *Citellus* reacted like a poikilothermic organism during the onset of lethargy, when between T_b of 35° and 15° C the arterial pH increased. At very low T_b it was lowered again to its "normal" level. In reality an acidosis developed (Person 1952). In all other species too, during deep hibernation, arterial pH-values have been found which are much lower than can be expected from the shifted neutral point: 7.22—7.63 (Bartels et al. 1969, Malan et al. 1973). Malan, Arens and Waechter (1973) suggest that this respiratory acidosis may represent a new regulated state (pH 7.57) that is related to the degree of inhibition in the respiratory centre. The new set-point is connected with the rise in $[HCO_3]$ and the elevation of arterial P_{CO_2} (Clausen and Ersland 1968, Johansson and Senturia 1972 b, Kent and Peirce 1967, Malan et al. 1973). Diminished P_{CO_2}

has been observed in some cases at the beginning of decreasing T_b. The rise in ketone bodies (Baumber et al. 1971) is probably not correlated directly with the hibernation acidosis, but metabolic acids may modulate the increase of $[HCO_3]$. The arousal process leads to a temporary decrease in arterial CO_2-concentration and P_{CO_2}, as a consequence of the intensified ventilation, and to a development of metabolic acidosis (Ambid 1971, Clausen and Ersland 1968, Ferdmann and Feinschmidt 1934).

O_2-transport: All data on O_2-levels in blood (vol%) depend finally on the concentration of hemoglobin. In accordance with the slower formation and the storage of erythrocytes, a hemodilution with a diminished O_2-transport capacity during hibernation was frequently observed (Barry 1971, Kayser 1961, Larkin et al. 1972, Nansal and Knoche 1972, Spurrier and Dawe 1973). In many cases however, within the same species, a hemoconcentration appears (Kayser 1961, Lyman and O'Brien 1963, Suomalainen and Rosokivi 1973), probably caused by the repartitioning of water. Sometimes the values for these parameters were unchanged (Kayser 1961, Wenberg and Holland 1973 c). Therefore the hemoglobin concentration plays no role in maintaining hibernation.

In awake hibernators, the arterial and venous partial pressure of O_2 may be lower than in other mammals (Musacchia and Volkert 1971 a, Volkert and Musacchia 1970). During hibernation, some values were low (Johansson and Senturia 1972 b, Musacchia and Volkert 1971 a) and some were high. Generally, the oxygen transport to the tissues during torpor seems to be optimal.

The affinity of hemoglobin for oxygen in awake hibernators is at least as high as in other mammals. The O_2-dissociation curves agree with expectations (Kayser 1961, Tucker 1968). In mountain species they are somewhat steeper (Bullard et al. 1966). The hemoglobin structure during hibernation is unchanged (Addis et al. 1973, Bullard et al. 1966). Owing to the cooling of blood during hibernation, the oxygen dissociation curve is shifted to the left (Clausen and Ersland 1968, Musacchia and Volkert 1971 a). In the hedgehog, however, an additional seasonal shift to the left was observed (Bartels et al. 1969). It is not clear if this is connected with the rise of 2,3-diphosphoglycerate in the erythrocytes (Hensel et al. 1973). The influence of temperature on the oxygen dissociation curve can be characterized by the O_2-affinity-temperature coefficient ($\Delta \log P_{O_2} / \Delta T$) at a 50 % oxygen saturation. This value is extremely low in the hibernating hedgehog (0.0161—0.0167), while in all other species it is normal (0.0215—0.0229). Therefore a specific alteration of the dissociation curve is not typical of hibernation (Musacchia and Volkert 1971 a).

The Bohr effect is very small at low T_b during hibernation (Clausen and Ersland 1968). Therefore it is unlikely that the hibernation acidosis improves the O_2 distribution to the tissues markedly. Perhaps the loss of toxicity of pure oxygen during hibernation (Popovic et al. 1964) depends not only on the low metabolism but also on the steepness of the O_2-dissociation curve. Generally, during torpor the tissues are hypoxic.

The arousal process in its first phase is marked by a rise in the tidal volume and in the second phase by a rise in respiratory frequency (Malan et al. 1973). However a hypoxemia develops (Ambid 1971). The increasing temperature and the Bohr effect produce a shift in the O_2-dissociation curve to the right and improve the oxygen uptake in the tissues. Therefore even the P_{O_2} in the abdominal cavity of the hedgehog increases (Barr and Silver 1972).

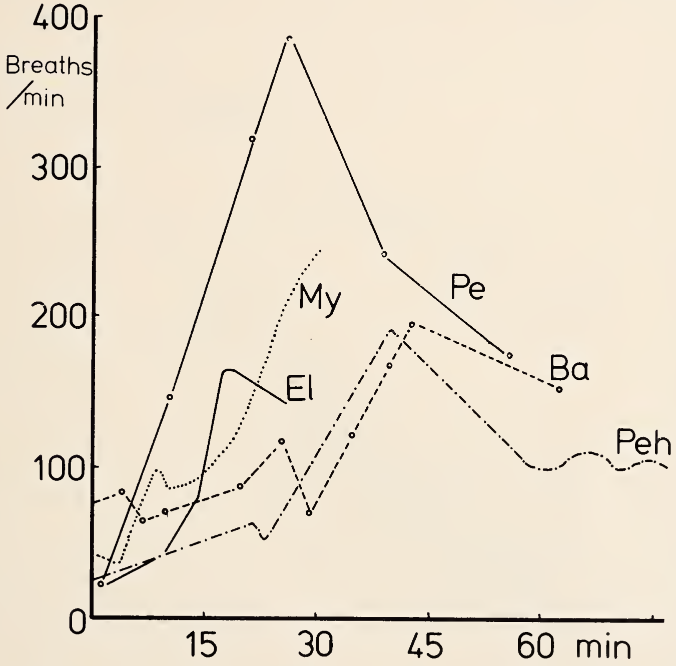

Fig. 16: Breathing rate during arousal from torpor. Pe = *Perognathus longimembris* (Bartholomew and Cade 1957), Peh = *Perognathus hispidus* (Wang and Hudson 1970), Ba = *Baiomys taylori* (Hudson 1965), El = *Eliomys quercinus* (Herter 1956), My = *Myotis myotis* (Herter 1956).

Summary: During hibernation, the respiratory centre is inhibited. Its excitability is adjusted to maintain an arterial acidosis with a pH 7.57. Simultaneously the sensitivity of the effectors (diaphragm) increases. The O_2 transport shows no special adaptations for torpor. Therefore the tissues are hypoxic, in spite of the improved O_2 uptake by the lungs.

VI. Energy Metabolism

Energy balance. The metabolism of awake hibernators (also of bears and badgers) during the hibernation season is lower than at other times of the year (Hildwein 1970, Kayser et al. 1969, Mletzko and Raths 1972 a). The yearly rhythm is temperature independent (Malan and Hildwein 1965, Mletzko and Raths 1972 a), but is correlated with the rhythms of motor activity and the rhythms of most endocrine glands. The decrease in basal metabolic rate (BMR) during winter probably is related to the lowered T_b (Herter 1956) even in the active state, and also to a greater sleepiness, but less so to the storage of adipose tissue (Hudson and Deavers 1973).

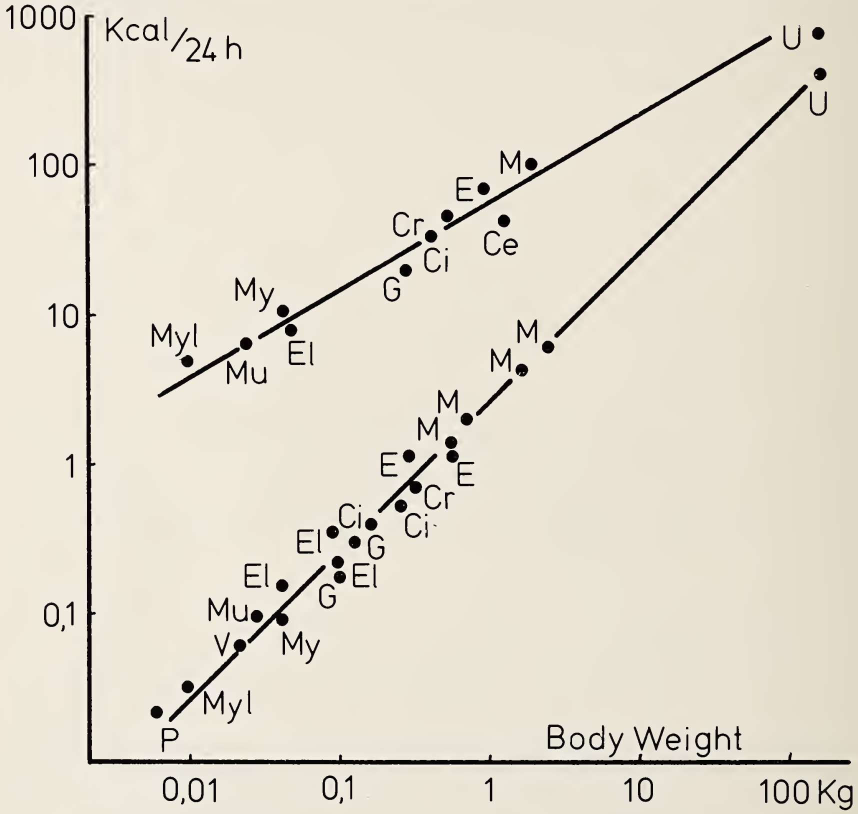

Fig. 17: Heat production (BMR) of different species of hibernators in summer (upper curve) and during hibernation (lower curve); adapted from Kayser (1961) and other authors. Ce = *Centetes ecaudatus*, Ci = *Citellus citellus*, E = *Erinaceus europaeus*, El = *Eliomys quercinus*, G = *Glis glis*, M = *Marmota marmota*, Mu = *Muscardinus avellanarius*, My = *Myotis myotis*, Myl = *Myotis lucifugus*, P = *Pipistrellus pipistrellus*, U = *Ursus americanus*, V = *Vesperugo noctula*.

At the onset of hibernation, the O_2-consumption at first decreases slowly, but then more rapidly between 30°—20° C T_b ($Q_{10} = 5$) (Henshaw 1968). In numerous articles Kayser has given values on metabolism during deep torpor. The metabolism in small species is only $^1/_{100}$ of the summer basal metabolic rate, in medium sized hibernators $^1/_{30}$ (Kayser 1961, 1964 a) and in the bear $^1/_2$—$^1/_3$ (Hock 1960). Similar values were found in lethargic birds (Lasiewski et al. 1967). As the minimal metabolism in different species occurs at different T_b, Kayser attempted to relate all results to a T_b of 10° C using van't Hoffs rule. In summary, the following formulas were obtained (W = weight):

Basal metabolic rate (BMR) during summer
$Q\ [\text{Kcal/animal} \cdot 24\ \text{h}] = 63.6\ W^{0.62}$
(Kayser 1964 a)

Hibernation, minimal metabolic level at different T_b
$Q = 2.16\ W^{1.02}$
(Kayser 1964 b)

Hibernation, referred to T_b 10° C
$Q = 2.09\ W^{0.69}$
(Kayser 1964 b)

Obviously at 10° C metabolism is always related to the surface area. This problem also has been discussed by South and House (1967), Hudson (1969), Swan (1971) and Swan et al. (1969). The arousal from torpor is combined with an enormous increase in O_2-consumption, in the course of which the curve of O_2-uptake is bell shaped (Hammel et al. 1968, Kayser 1961). In many investigations it has been shown that the BMR of awake hibernators is always lower than that of other mammals and birds (Henshaw 1968, Hildwein and Kayser 1970, Hudson 1967, 1969, Hudson and Deavers 1973, MacMillen and Trost 1967 a). However, there are contradictory results (Mletzko and Raths 1972 a). If one considers that all quantitative statements such as the Brody-Kleiber formulas are of statistical nature and are valid in large experimental numbers only, and that the BMR clearly shows seasonal alterations, conclusions can be made only with extreme caution. Probably Hudson (1969) may be right that the level of BMR is no criterion of the ability to hibernate.

Qualitative aspects of metabolism: The biochemical aspects of metabolism can only be outlined in this review. The respiratory quotient (RQ) during hibernation is 0.7 (Kayser 1961, 1964 b). The significance of lower values (0.60—0.65) is doubtful (Nelson et al. 1973, Yousef et al. 1967). During the arousal process, an oxydation of carbohydrates is added to the lipolysis, so that the RQ — depending on the species and the T_b — lies between 0.8—1.0 (Kayser 1961, 1964 a).

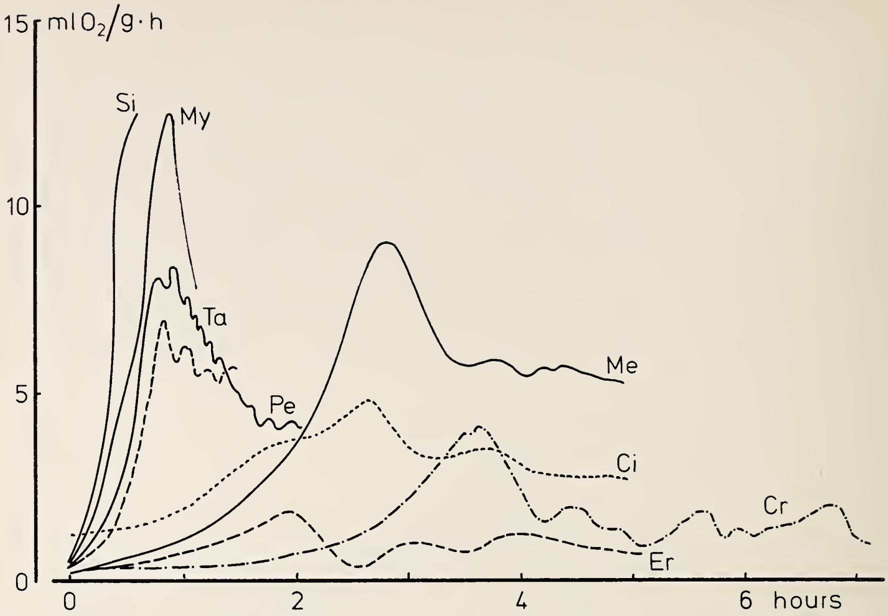

Fig. 18: Oxygen consumption during arousal from hibernation (T_a 5°—6° C); note that the chief peak decreases concomitant with increase of body weight. Si = *Sicista betulina,* single ind. 10 g (Johansen and Krog 1959), My = *Myotis myotis,* average curve, 24.4 g (Mejsnar and Jansky 1970), Pe = *Perognathus hispidus,* single ind. 40 g (Wang and Hudson 1970), Ta = *Tamias striatus,* single ind. 95 g (Wang and Hudson 1971), Me = *Mesocricetus auratus,* single ind. 90 g (Lyman 1963), Ci = *Citellus mexicanus,* single ind. 200 g (Neumann and Cade 1965), Cr = *Cricetus cricetus,* single ind. 340 g (Raths unpubl.), Er = *Erinaceus europaeus,* single ind. 700 g (Suomalainen 1962).

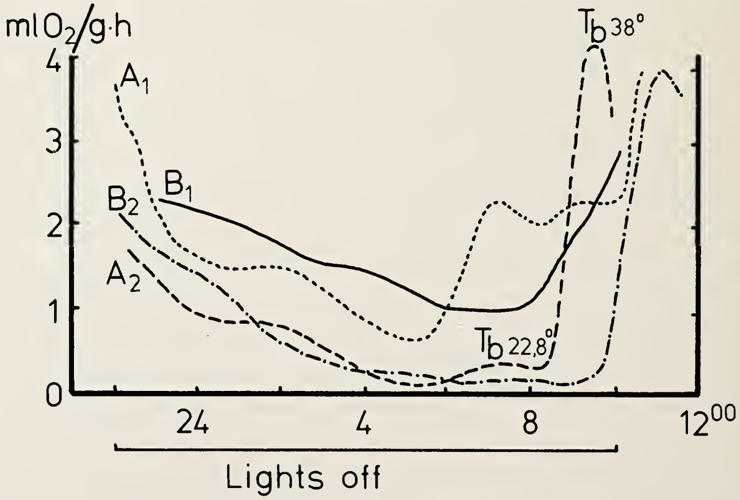

Fig. 19: Daily torpor of two mouse birds *(Colius striatus)* during consecutive nights (T_a 19.2° C). Three of the four arousals were spontaneous, but one (A_2) was caused by the attachment of the cloacal thermocouple. Adapted from Bartholomew and Trost (1970).

Short days during autumn as well as low temperatures stimulate the prehibernatory lipogenesis in adipose tissue and also raise the fat content of the blood (Burlington et al. 1969, Denyes and Baumber 1964, Lynch and Folk 1971). Since special proteins for transporting fat exist (Wenberg and Holland 1973 a), the fat content of many other tissues increases as well (Ewing et al. 1970, Galster and Morrison 1966, Krulin and Sealander 1972, Poche 1959, Wenberg and Holland 1973 a, Zimny et al. 1964). However, a similar storage of fat before the onset of aestivation suggests that internal control mechanisms are decisive, especially the decrease of the sympathetic activity (Scheufler and Raths 1967). During lipogenesis in autumn, and to some extent even during hibernation, the pentose shunt plays a very important role (27 %—86 %), while the Krebs-cycle is less involved (Castex 1972, Olsson 1972). The seasonal adaptations of the intermediary fat metabolism can be explained partially by alterations in the activity of enzymes (Denyes and Baumber 1964, Whitten and Klain 1969). During hibernation, the serum lipids, free fatty acids, cholesterol and phospholipids usually show a high concentration (Nelson et al. 1973, Suomalainen and Saarikoski 1971, Wenberg and Holland 1973 a), but seldom a low one (Platner et al. 1972, Wenberg and Holland 1973 a). In some species lipogenesis may continue during torpor. In others it is inhibited (Whitten and Klain 1969). In any case, an increased lipolytic activity is prominent (Chaffee et al. 1966, Olsson 1972, Suomalainen and Saarikoski 1971). Low T_i in the brown adipose tissue stimulates in vitro the oxydation of palmitic acid rather than oleic acid (Dryer et al. 1970). This explains the diminished saturation and the lowered melting point of fat in different organs during hibernation (Ambid 1971, Ewing et al. 1970, Laukola and Suomalainen 1971, Minor et al. 1973, Platner et al. 1972). Contradictory results from Wells et al. (1965) show however that not all stored fats act in the same manner.

During arousal an explosive lipolysis takes place. However, this process will be discussed, together with the special role of brown fat, in the section on temperature regulation.

The level of glycogen in the liver, musculature, heart and even in motor structures of the central nervous system is increased during hibernation (Castex 1972, Gabe et al. 1964, Mayer W. V. 1960, Oksche 1961, Saarikoski and Suomalainen 1970, 1971, Wolff 1970). The storage certainly takes place before the onset of torpor, but in some species it may even occur during lethargy (Forssberg and Sarajas 1955, South and House 1967, Whitten and Klain 1969). Glycogen is mobilized especially during arousal (Cossel and Wohlrab 1964, Saarikoski and Suomalainen 1970).

Seasonal alterations in blood glucose concentration are doubtful and are difficult to substantiate (Agid and Sicart 1969, Castex 1972). At the beginning of the disposition for hibernation or aestivation, a hypoglycemia develops (Gabe et al. 1964), which becomes stronger during decreasing T_b.

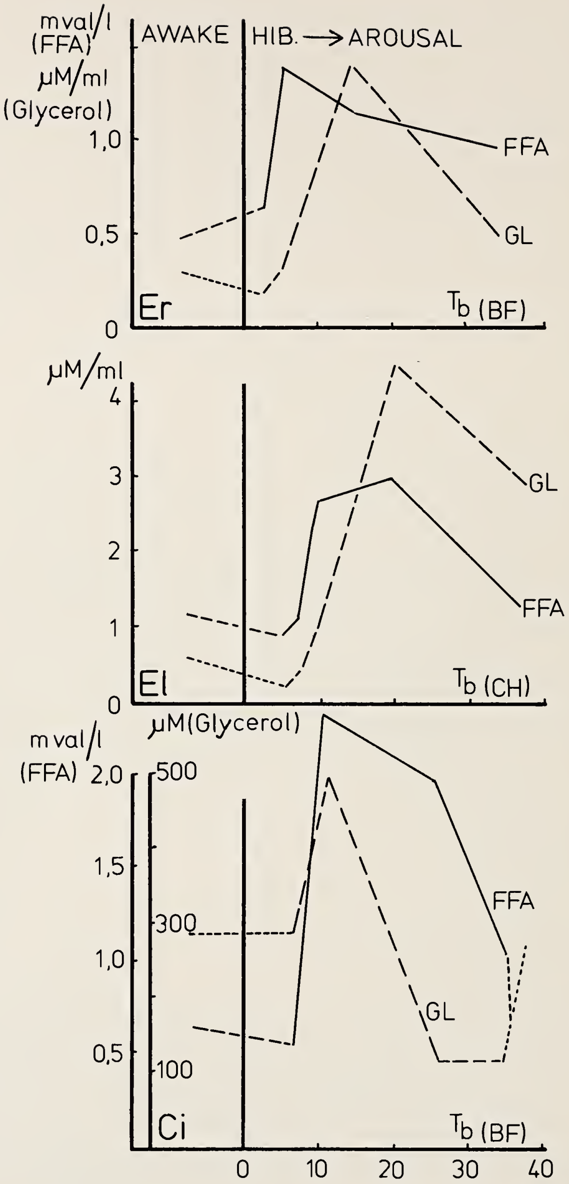

Fig. 20: Arousal from hibernation. Dependence of blood free fatty acids (FFA) and glycerol on the core temperature during rewarming. Remember that velocity of rewarming is different in the three species. Er = *Erinaceus europaeus*, serum (Suomalainen and Saarikoski 1967), El = *Eliomys quercinus*, plasma, average curves (Ambid 1971), Ci = *Citellus undulatus*, plasma (Galster and Morrison 1975); BF = brown fat, CH = chest.

A high T_b during hibernation is accompanied by stronger hypoglycemia than when T_b is low (Raths 1961). Otherwise, the blood sugar level is normal (Spurrier and Dawe 1973) or raised (Raths 1961). The hypoglycemic phase has complex causes: An instinctive reduction in food intake, a prehibernatory activation of synthesis of glycogen and fat by insulin (Scheufler and Raths 1967), and an inhibited glycogenolysis as a result of the decreasing sympathico-adrenergic tone (Raths 1953, 1957, Scheufler and Raths 1967). Because of depressed kidney function, glucosuria (Zimny and Bourgeois 1960) seems to be of low importance. The hibernatory normo- or hypoglycemic phase also has a complex nature. In spite of a specific inhibition of the enzymes of glycogen metabolism, transformation of glycogen into glucose is possible (South and House 1967), perhaps by an increase in the sympathetic tone during deep hibernation (Scheufler and Raths 1967). On the other hand, the tendency to hyperglycemia is supported by the diminished transformation of sugar into fat and glycogen, by the increase of gluconeogenesis and by a diminished use of glucose (specific inhibition of enzymes and low T_b) (Burlington and Klain 1967).

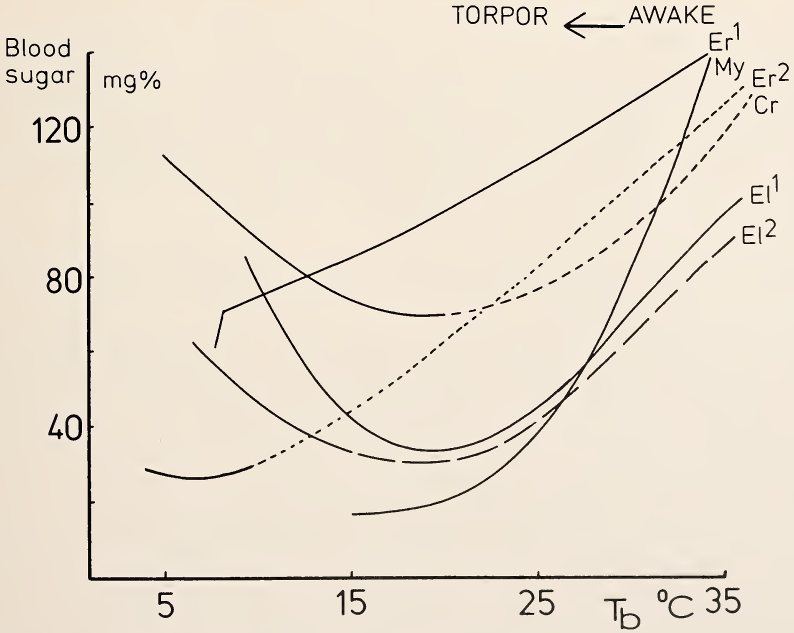

Fig. 21: Hypoglycemia during hibernation and aestivation (average curves); Er¹ = *Erinaceus europaeus*, hibern. (Sarajas 1967), Er² = *Erinaceus europaeus*, hibern. (Clausen 1964), Cr = *Cricetus cricetus*, hibern. (Raths 1961), My = *Myotis lucifugus* and *M. grisescens*, hibern. (Dodgen and Blood 1956), El¹ = *Eliomys quercinus*, hibern. Nov. Dec. (Ambid 1971).

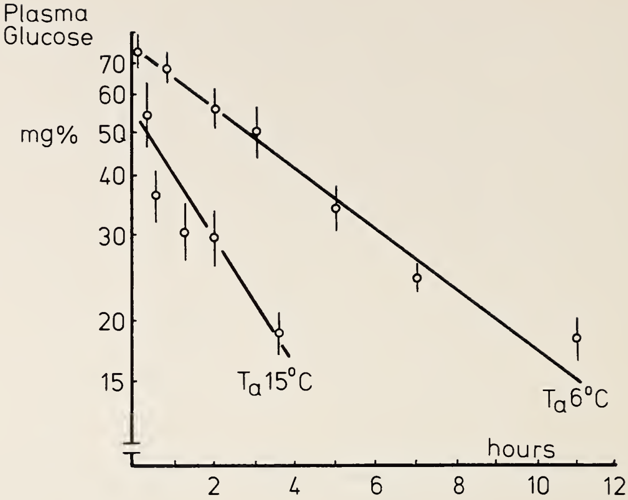

Fig. 22: Drop of plasma glucose level in the hibernating garden dormouse at different ambient (and body-) temperatures. Adapted from Ambid (1971).

However, homeostasis of the blood sugar level may be difficult to maintain during hibernation (Raths 1961). After all, in golden hamsters, survival time during helium-induced hypothermia is increased if one prevents the decrease of liver glycogen and blood glucose (Prewitt et al. 1972). Glucose can be absorbed from the intestine during hibernation (Musacchia and Westhoff 1964, South and House 1967).

During arousal, a short hypoglycemic phase is followed by a rise in blood sugar to normal or even above normal levels (Heldmaier 1969, Saarikoski and Suomalainen 1970).

Generally, the energy supply for the formation of ATP during hibernation occurs mainly by fat catabolism and to a small extent by sugar catabolism. RQ-values between 0.6—0.7 suggest that some fat is transformed into carbohydrates. Most biochemists agree that during the onset of hibernation, there is no lack of energy-rich phosphates (ATP, phosphocreatine) and that the ATP-forming systems in awake hibernators are as effective or even more effective than in other mammals (Kristoffersson 1961). However during continuous hibernation, the synthesis of the highenergy phosphates does not keep up with its use completely (Ferdman and Feinschmidt 1934, Kristoffersson 1961). — During arousal, a further decrease in energy-rich phosphates in various organs occurs (Zimny 1964).

The efficiency of the respiratory chain for the formation of the ATP during hibernation is very good at T_i between 6°—37° C (Kayser 1964 b, Roberts and Chaffee 1973). Partially this is the result of an increase

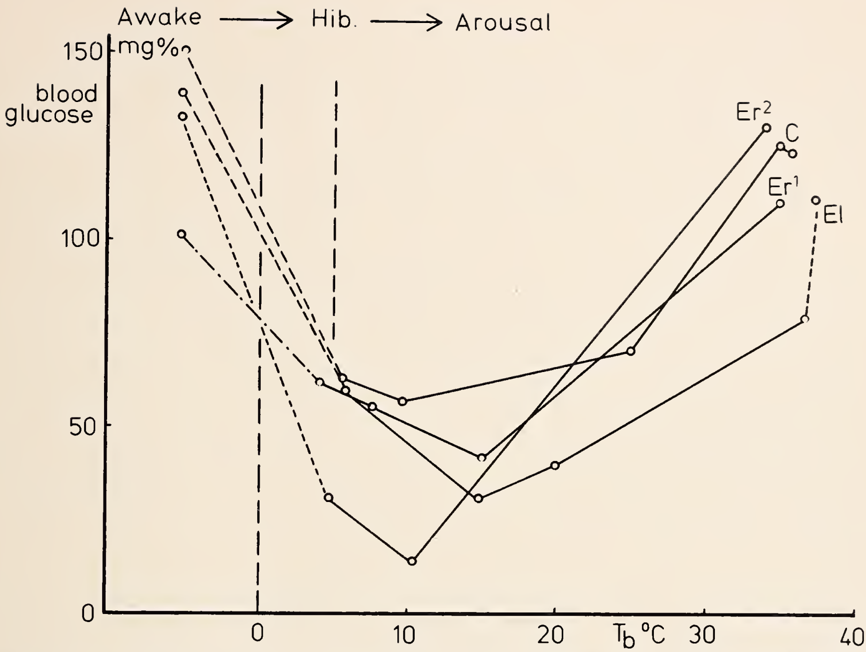

Fig. 23: Dependence of blood glucose on core temperature during arousal from hibernation. El = *Eliomys quercinus,* plasma, chest temperature (Ambid 1971), C = *Citellus undulatus,* plasma, brown fat temperature (Galster and Morrison 1975), Er¹ = *Erinaceus europaeus,* whole blood, interscap. temperature (Saarikoski and Suomalainen 1970), Er² = *Erinaceus europaeus,* plasma, rect. temperature (Clausen 1964). Average curves.

in number and an enlargement of the individual mitochondria in different tissues (Cossel and Wohlrab 1964, Umahara 1968) and of the intramitochondrial accumultation of substrates and enzyme material (Poche 1959). By an improved coupling of ATP formation to the respiratory chain, the O_2-consumption of tissues during hibernation (in respect to the decreased temperature) should be the same or even lower than that during the normothermic state. A lowered O_2-consumption should occur also if the tissues change from aerobic to anaerobic metabolism. From the unchanged or even increased P/O-ratio (liver, brain) one can conclude that there is a good coupling in the tissues.

In vitro studies have had very different results, depending on the organs that are used, on the methods and on the T_i. Generally, for comparable T_i's in liver and brain tissues, a decreased O_2-consumption was usually found; in heart and skeletal muscles it was increased, in kidneys and in brown fat unchanged (Denyes and Hassett 1960, Horwitz and Nelson 1968). Contradictory results are also known. There even seem to be differences within a species. In several cases a flattening of the Q_{O_2}-temperature curve was observed in tissues of lethargic animals, which corresponded with an adaptive reduction of the activation energy; however this is not always the case (Kayser 1960, 1961).

Several investigators have shown that tissues (brain, heart) of hibernating species have fundamentally greater possibility for anaerobic glycolysis than other mammals. This should be of importance for the hypoxic conditions during torpor (Andjus et al. 1971, Burlington and Klain 1967, Johansson 1967, Johansson and Senturia 1972 a, Kayser 1960, Kayser and Malan 1963, South and House 1967, Willis 1968). In spite of this fundamental possibility, during hibernation, several enzymes in glycolysis are inhibited specifically (Smally and Dryer 1967), but not all of them. From numerous biochemical investigations it can be supposed that during hibernation the pyruvate that is produced is transformed into lactate and finally back into carbohydrate (Burlington and Klain 1967, Burlington and Sampson 1968, Larkin et al. 1967, Musacchia and Saunders 1969, Olsson 1972).

The numerous studies on enzymes of the Krebs-cycle and of the respiratory chain also support the conclusion that several steps of oxydative metabolism are inhibited specifically during hibernation (Chaffee et al. 1966, Olsson 1972, Roberts and Chaffee 1973, Whitten and Klain 1969). On the other hand, several properties of oxydative metabolism at low temperatures resemble that of poikiotherms more than of mammals (Niwelinski et al. 1969). However, decrease of temperature dependence of some physiological functions (heart rate, O_2-uptake), as well as some biochemical and histochemical investigations suggest that true metabolic adaption to low T_b takes place probably by an accumulation of certain enzymes and by lowering of the activation energy (thermal increment) for several metabolic reactions, either by cold adaptation or by the development of the seasonal hibernatory disposition. As well, phylogenetic (hereditary) adaptations can be shown to be involved (Roberts and Chaffee 1973, South and House 1967, Suomalainen and Ahlström 1970).

Summary: The lowered energy metabolism in awake hibernators probably does not depend on their ability to enter torpor. During hibernation, the main energy source is fat. ATP-formation partially occurs by more efficient coupling and partially by an acceleration of anaerobic glycolysis. The transformations in metabolism take place either by specific inhibition of enzymes, or by a decrease in the temperature sensitivity of enzymes. In this manner the metabolism is lowered quantitatively (O_2-saving) and its economy is improved.

VII. Anabolism

Naturally catabolism and anabolism cannot be separated from each other accurately. Anabolism certainly does not play a fundamental role during torpor. However, some different physiological functions, which depend especially on cell division and protein synthesis, are markedly changed during hibernation.

Compared with other mammals, hibernators in spite of the greater resistance of their protein synthesis to the effects of cold, show a decrease in the protein content of blood and of several organs (after a maximum in autumn) during hibernation (Hoo-Paris and Garcin 1970, Kirkebö 1968, Kristoffersson and Broberg 1970, Olsson 1972). The shift of the protein metabolism towards catabolism is connected with a disturbed function of the ribosomes (Whitten 1971) as well as with a diminished synthesis and content of RNA and DNA in the organs (Adelstein and Lyman 1968, Cossel and Wohlrab 1964). As a consequence of this, a significant increase in albumin appears, while the gamma-globulins and sometimes the beta-globulins of serum reach a minimum during hibernation (Kayser 1961). These changes lead to a decrease in the sedimentation rate of blood (Pavlovic 1964) and also to immunological depression (Fokken and Jaeger 1975). As well, during hibernation the spectrum of the free amino acids in blood and in the organs is changed (Kristoffersson and Broberg 1968, 1970, Nelson et al. 1973). As a result, the decrease in glutamic acid in the brain and the increase of gamma-amino butyric acid could be of particular importance in the changes of excitability.

In connection with the depressed renal function, the diminished breakdown of amino acids during hibernation leads to an increase in their concentration in urine (Ferdmann and Feinschmidt 1934, Kristoffersson and Broberg 1968), to a decreased urea production (Kristoffersson 1963) and to lowered urea concentration in blood (Moy 1971, Nelson et al. 1973). On the other hand, urea and ammonia are gradually stored in the blood and in the tissues (Clausen 1964, Kristoffersson 1963, 1965, Kristoffersson and Broberg 1970, Tempel and Musacchia 1975).—The reactivation of different enzymes during arousal (Whitten and Klain 1969) leads to a strong protein breakdown (which aids thermoregulation), followed by an increase of free aminoacids (Kristoffersson and Broberg 1968) and ammonia in the blood.

During hibernation, cell division in epithelial tissues is depressed (Mayer, W. V. 1960) as well as erythro-, leuco- and lymphopoiesis (Kayser 1961), the ability of the liver to regenerate (Thomson et al. 1962) and of tumors to grow (Popovic et al. 1969, Thomson et al . 1962). Destruction of cells occurs a little faster than their production (Galster and Morrison 1966). Therefore, in spite of the prolonged life span of the erythrocytes (Larsen 1968), and in spite of their increased resistance to hemolysis

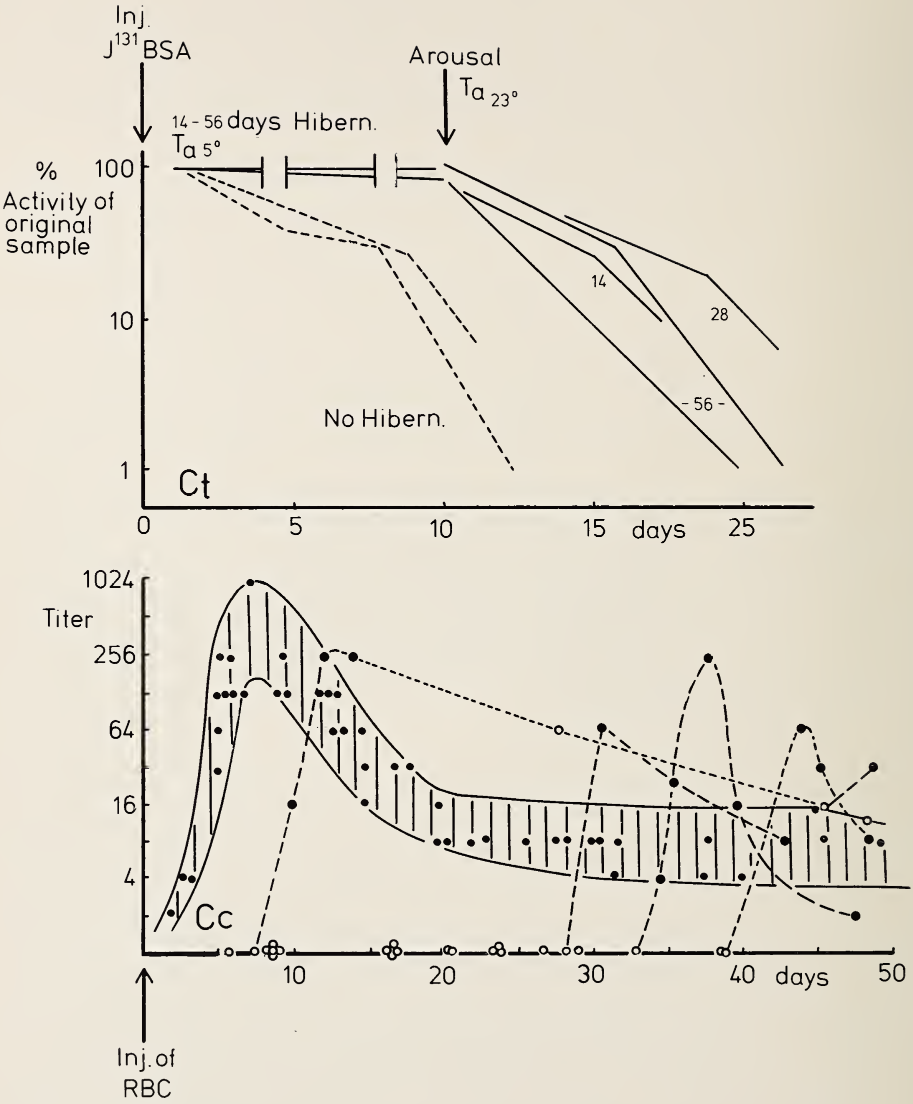

Fig. 24: (Top) Disappearance of antigen J^{131}-bovine serum albumin (BSA) in the waking state, during hibernation and after arousal in four *Citellus tridecemlineatus* (Ct). Hibernation 56, 28, 14 days. Adapted from Jaroslow and Smith (1964). (Bottom) Appearance of immune hemagglutinins in the serum of ground squirrels *(Citellus citellus* = Cc) after injection of rabbit red blood cells (RBC) at the time zero. Adapted from Andjus et al. (1964).

(Dawe and Spurrier 1972, Spurrier and Dawe 1973), diminished numbers of erythrocytes are found during hibernation. Owing to the depressed metabolism, the inhibited mitotic activity and the hypoxic situation, the effect of ionizing radiation on the tissues, is relatively small during hibernation (Musacchia et al. 1971 b). Details can be found in the work of Popovic et al. (1969).

Torpor protects the organism against infections with *Trichinella, Trypanosoma, Tryponema,* bacteria, viruses and also against the effect of venoms and carcinogenic substances (Chute 1964, Kalabukhov 1969, Kayser 1961). The resistance is the result of the reduced metabolism during hibernation, as well as the fact that the reproduction of parasites is more inhibited than the immunity mechanism of the host. During arousal, virulence as well as the capacity for resistance increase rapidly.

The **production of antibodies** during hibernation is extremly low or even non-existent (Jaroslow 1971, Larsen 1971), but during a short interruption of torpor (rewarming) may recommence immediately. This may be the essential reason why positive results have been recorded for the production of antibodies during torpor (Kayser 1961). Naturally, owing to the depressed immunological reactivity, antigens are eliminated from the blood extremely slowly (Chute 1964, Larsen 1971). The immunological depression is the result of the low T_b, of the decrease in gammaglobulins caused by their rapid destruction, as well as the result of an inhibited proliferation of cells with a capacity for antibody formation (Jaroslow 1971). At the same time, an unknown factor of the brown adipose tissue (maybe, a corticosteroid) perhaps develops an inhibitory action on the antibody formation of the spleen (Sidky et al. 1969).

The **mechanisms of phagocytosis** (RES, leucocytes) are less inhibited during hibernation than antibody formation (Schmidt 1967). In spite of earlier speculations, the lymph nodes are small and inactive and the mobility and the phagocytosis by the lymphocytes are diminished, in agreement with inhibition of lymphopoiesis (Slonim 1971). The circulatory changes during hibernation always lead to a leucopenia (Larkin et al. 1972, Nansal and Knoche 1972, Pavlovic 1964, Raths 1953, 1957, Spurrier and Dawe 1973, Suomalainen and Rosokivi 1973), in the course of which lymphocytes and eosinophils accumulate in the intestinal wall (Henriksen 1972, Inkovaara and Suomalainen 1973). The transition from sleep to hibernation is marked by a relative lymphocytosis, but at low T_b, granulocytes are predominant (Raths 1953, 1956, 1964, Suomalainen and Rosokivi 1973, Wenberg and Holland 1973 c).

The **blood clotting** is closely connected with the protein metabolism. The blood clotting time in hibernation and aestivation at comparable T_i is always prolongated two or threefold. Yet it is not quite clear, which of the factors accelerating the clotting, are diminished fundamentally and which inhibitory factors are increased decisively. Probably thrombocytopenia plays a role, whereby the platelets accumulate in various tissues as a result of the slowed circulation (Sarajas and Halinen 1970). Another reason for depression of clotting is the reduction of the prothrombin concentration in blood. Whether the levels of factors V and VII decrease is uncertain (Raths and Perlick 1953). Also the reduction of the factors VIII, IX, X and of fibrinogen similarly may be dependent upon hibernation (Wenberg and Holland 1973 c). The rise in antithrombin-activity during hibernation is based on an increased heparin level, or the heparin Co-factor activity in blood, and probably on antithrombin II and III. Whether the mast-cells play a role in this is questionable. These cells accumulate, again as the result of slowed circulation during hibernation, in many very different tissues, whereas they decrease or remain constant in others (Henriksen 1972, Hjelman 1956). Changes in the fibrinolytic system (Johansson and Senturia 1972 a) probably are without significance in the prolongation of clotting time.

Summary: During hibernation, many alterations in the immunity and blood clotting mechanisms are based on the inhibition of anabolic metabolism, especially of cell division and protein synthesis. As well, a change in the distribution of blood cells owing to the slowed circulation plays a role.

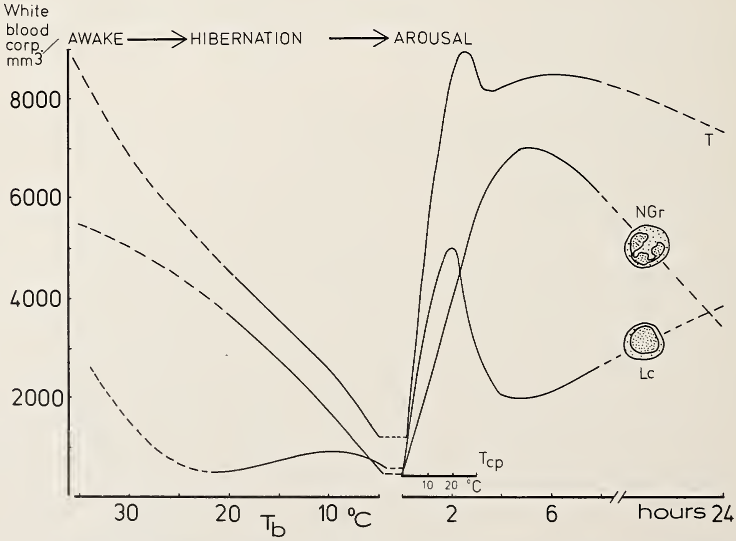

Fig. 25: Change of white blood cell count during hibernation and arousal in the European hamster. Average curves; NGr = neutrophils; Lc = lymphocytes; T = total; Tcp = cheek pouch temperature; from Raths (1956, 1961).

VIII. Hormones

Generally, the endocrine activity during hibernation depends on many factors, for example, the annual rhythm, cold adaption, T_b during torpor as well as the frequency of periodic arousal. An annual cycle of endocrine activity could be proved in most hibernators. A progressive involution of adenohypophysis, gonads, thyroid and adrenal cortex from summer to late in autumn and a slow reactivation during winter was found generally (Gabe et al. 1964, Hensel et al. 1973, Kayser 1961, Popovic 1960, Raths 1975).

A production of hormones during low T_b in hibernation is hardly possible. However, there are some references which suggest that hormones can be secreted during hibernation, such as those involved in changes of mineral and carbohydrate metabolism, which depend on T_b. Several investigators deny any hormonal regulation during hibernation. Certainly, an extirpation of endocrine glands does not induce hibernation because the resulting metabolic disorder prevents the necessary instinctive behaviour. Destruction of the thyroid or adrenal cortex even prevents the onset of hibernation, while replacement of the missing hormones allows it to occur again (Canguilhem and Malan 1969, Popovic 1960). Further, total endocrine inactivity during winter would impede or even prevent arousal after entrance into torpor because, during arousal, the whole endocrine system successively is activated (Boulouard 1972, Nunez et al. 1974, Portius and Raths 1957).

Thyroid gland: The autumnal involution of the thyroid gland is followed by a slow reactivation of the gland late in winter, owing to the increased activity of the basophilic TSH-cells of the pituitary (Dörfler 1971, Gabe et al. 1964, Smit-Vis and Smit 1966). However, histological investigation in bats has shown that the increased activity is related to the secretion of the hormone but not to an accelerated synthesis (Nunez 1971). Autumnal decrease of the T_a may lead to a temporary increase in thyroid activity which, however, does not impair hibernation and winter sleep (Nelson et al. 1973, Tashima 1965, Yousef et al. 1967). Furthermore, the capacity of the thyroid for incorporation of J^{131} during hibernation is very high (Wenberg and Holland 1973 b). Therefore, the apparent "seasonal" involution of the gland and hormone storage seem not to be the cause of hibernation, but the results (Tashima 1965); in this connection, the hormonal level in the blood is reported to be low or high as well. Contradictory findings regarding the positive or negative reaction of the thyroid gland (and suprarenal cortex) to cold (Popovic 1960, Tashima 1965) may be explained by the presence or absence of a readiness for hibernation. Species differences need not be considered.

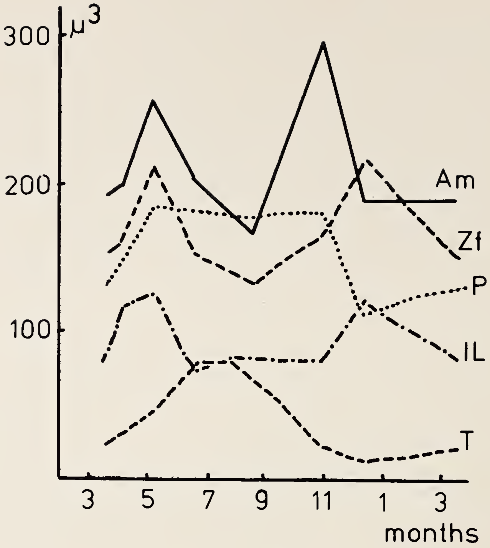

Fig. 26: Seasonal changes of endocrine glands (volumes of nuclei) in bats (*Myotis myotis, Rhinolophus hipposideros*). Adapted from Dörfler (1971). Am = adrenal medulla, Zf = zona fasciculata, P = parathyroid, IL = islets of Langerhans, T = thyroid.

C-cells of the thyroid: The parafollicular C-cells contain calcitonin and serotonin. During hibernation they are inactive and store the hormones (Dörfler 1971, Nunez and Gershon 1972). During aestivation the number of the cells is increased. In marmots an annual cycle has not been proved clearly. The lack of calcitonin could contribute to hypercalcemia and hypermagnesemia during hibernation (Stoeckel et al. 1967).

Parathyroid: Histological studies have shown a prehibernatory activity of the gland. Studies of Ca-metabolism seem to confirm this. The annual cycle of parathyroid activity is inverse to the rhythm of the gonads (Kayser 1961), but identical with the C-cell activity (Dörfler 1971).

Pancreas: Based on earlier studies of Suomalainen and his co-workers (1955), it was concluded that insulin plays a major role in inducing hibernation. More recently, this has been questioned (Laurila and Suomalainen 1974, Popovic 1960). The histological evidence of an activation of beta-cells is probably related to the autumnal storage of glycogen and fat—but not directly to the torpor. During hibernation there is no activity in beta-cells (Kayser 1961, Smit-Vis and Smit 1966). But such activity appears at the end of the hibernation season, as well as during arousal (Laurila and Suomalainen 1974, Portius and Raths 1957) and during cold stress in awake hibernators subjected to artificial hypothermia (Weber and Scheufler 1970). Insulin is stored during hibernation (Gabe et al. 1964, Portius and Raths 1957, Raths 1964, Scheufler and Raths 1967, Laurila and Suomalainen 1974, Thorell et al. 1972). It is definitely decreased or not detectable in the serum of lethargic hedgehogs (Laurila and Suomalainen 1974).

Glucagon is formed in the A-cells. During hibernation these cells are inactive, their nuclei do not swell before arousal in spring or during periodical arousals (Portuis and Raths 1957). Glucagon is stored during hibernation, but a small and continuous secretion probably takes place (Smit-Vis and Smit 1966).

Gonads: Studies of the sexual rhythms of hibernators are in agreement (Hoffman 1964 a, Kayser 1961, Saure 1969, Walin et al. 1968, Wimsatt 1969). With the exception of bats, torpor is inhibited during sexual activity (estrus) (Smit-Vis 1972) and lactation, perhaps because the different instinctive behavioural reactions are incompatible with each other. The same is true for the nocturnal lethargy in hummingbirds during the breeding season (Howell and Dawson 1954). Furthermore, pregnant ground squirrels, after a transfusion of blood with the "hibernation trigger", did not enter hibernation until they were separated from their litters (Dawe and Spurrier 1974). Autumnal reduction in sexuality and reactivation during winter involve the gonads (Popovic 1960, Saure 1969, Walin et al. 1968, Wimsatt 1969), the secretion of 17-ketosteroids (Bigelow et al. 1964, Kayser and Schwartz 1960), the gonadotrophins of the hypophysis (Skreb 1955), and the growth of follicles and Leydig cells as well as several secondary sex characteristics (Hoffman 1964 a, Senturia and Johanssen 1972, Walin et al. 1968). The completion of the hibernation season in spring is associated with a general sexual activation. Castration, therefore, can prolong the readiness for hibernation as can an extended exposure to cold, which delays the development of the gonads (Ambid 1971, Richoux and Legait 1975). In lethargic bats, activation of spermatogenesis and Sertoli-cells after application of FSH lasts 5—7 days (Herlant 1967). Timing of the autumnal commencement of hibernation and of the arousal in spring differs somewhat between males and females (Pengelly and Asmundson 1975, Walin et al. 1968), because of the different annual rhythms in the hypophysis. Therefore, readiness for hibernation in males occurs earlier than in females and young ones (Kristoffersson and Soivio 1967). There may be also a lack of the hibernation "trigger substance" in the young animals (Dawe and Spurrier 1974). In general, the hibernation season may be timed by gonadal activity (Richoux and Legait 1975).

Adrenal medulla: Determinations of volume and weight of adrenal glands are contradictory, partially because of the independent alterations in cortex and medulla during hibernation. In the European hamster, the allometric relation between body weight and adrenal weight is unchanged during hibernation (Scheufler and Raths 1967).

The highest levels of catecholamines are found in adrenals during summer (Pengelley et al. 1971). High levels also occur during the preparation for hibernation and at the end of hibernation season (Lew and Quay 1973). The autumnal rise in activity of the medulla is intensified by cold, but especially by the simultaneous involution of the thyroid (Canguilhem and Malan 1969). Measurements of enzyme activity have suggested that during autumn the transformation from noradrenaline to adrenaline is increased, while the sympathetic tone at the beginning of hibernation decreases (Johansson and Senturia 1972 a). During hibernation itself, the medulla probably is inactive (Gabe et al. 1964, Kayser 1961) and the hormones are stored (Lew and Quay 1973, Scheufler and Raths 1967). Even though the renal excretion of catecholamines during torpor is very low, their concentration in the adrenals is decreasing gradually, because of the low rate of synthesis. Simultaneously, the ratio of noradrenaline to adrenaline decreases (Smit-Vis and Smit 1966). The catecholamines are not directly involved in hibernation itself. After demedullation, hibernation is still possible (Petrovic 1960) and the readiness for hibernation is diminished only slightly (Hoffman and Hester 1965). However, during arousal the medulla is always activated (Kayser 1961). In the blood of ground squirrels *(Citellus suslicus)*, the concentration of catecholamines increases so much at T_b 15° C that the Straub-heart preparation shows a very strong positive inotropic effect. In contrast, blood of hibernating animals has no effect and blood from fully awake animals is only weakly effective (Turpayev 1948). Blocking the synthesis of noradrenaline in hibernating golden hamsters makes arousal impossible (Feist 1970).

Adrenal cortex: The zona glomerulosa (outermost layer) is increased in width and is probably more active during hibernation (Engel et al. 1957, Poche 1959). This change may account for the increased secretion of renin (Brown et al. 1971, Slonim 1971, Zimny and Levy 1971). The concentration of aldosterone in the adrenals, the renal excretion of aldosterone (Bloch and Canguilhem 1966), width and size of nuclei in the zona glomerulosa (Raths 1964), and the development of the reno-juxtaglomerular apparatus increase with the duration of hibernation and the weight loss of the animals (Kolpakov and Samsonenko 1970). The increased secretion of aldosterone probably counteracts the disturbed Na/K balance at low T_b.

The inner layers of the cortex (zona reticularis and fasciculata) show an autumnal activation by cold (Dörfler 1971, Smit-Vis and Smit 1966), and at the same time, the concentration of 17-hydroxy corticosteroids in plasma rises. During hibernation the activity of the gland decreases, and the level of the hormones in blood declines (Gabe et al. 1964). With continuing hibernation, the inner layers of the cortex increase in width, and the concentrations of the corticosteroids in the gland and in blood (Boulouard 1972, Gabe et al. 1964) as well as the renal excretion of hormone increase. Under the same conditions in the garden dormouse, the ratio of cortisol to corticosterone is increased (Boulouard 1971). All these changes indicate a progressive activation by the hypophysis that is correlated with the end of the hibernation season.

In vitro experiments with adrenal glands form the garden dormouse and from ground squirrels have shown that during hibernation and at low T_b the gland cannot be activated (or only slightly) by ACTH (adrenocorticotrophin) (Boulouard 1972). On the other hand, the cortex of hibernating *Citellus* reacts markedly to an application of angiotensin II, suggesting that depletion of aldosterone during hibernation occurs by this mechanism (Kolpakov and Samsonenko 1970).—During arousal the activity of the adenohypophysis increases, and also the activity of the ACTH-producing cells (Gabe et al. 1964). Thus the inner cortex becomes activated and the concentrations of cortisol and corticosterone in blood are raised.

Neurohypophysis: Most authors agree that hormone (ADH) is stored during hibernation and that this storage is accelerated during autumn by a short photoperiod (light time) and by cold (Yurisova 1971). In the same way, in contrast to earlier opinions, one can interprete the storage of glycogen in the supraoptical-paraventricular system (Wolff 1970) as indicating a resting stage of these structures during hibernation (Suomalainen and Walin 1972). The stored hormone is secreted only during arousal (Gabe et al. 1964). Simultaneously, the ability to concentrate urine is re-established.

Summary: The endocrine glands of hibernators show an annual cycle with an autumnal involution, a transitory period of increased activity just before entering torpor and a reactivation late in winter. Sexual inactivity is a pre-condition for hibernation, while the involution (state of storage) of the other glands seems to be the result of the torpor itself. During hibernation, reactivation is possible if there is a demand for stabilizing the mineral metabolism at low T_b (parathyroid, zona glomerulosa) to start the arousal (adrenals, endocrine pancreas, thyroid).

IX. Temperature Regulation

Thermoregulatory properties: Awake hibernators react against cold not only by decreasing thermal conductance (piloerection, vasoconstriction), by a rise in metabolism (shivering and non-shivering thermogenesis), by behavioural patterns, but also by a decline in core temperature (Davis 1970, South et al. 1972 b, Weigold 1973). Because the former thermoregulatory abilities correspond with those of other mammals, certain instabilities of T_b (Eisentraut 1955, 1956, Herter 1956, Hock 1960) and "insufficiences" of physical and chemical regulation (Hildwein 1970, Kayser 1961, Mills et al.

1974, South et al. 1975) are by no means indicators of a primitive state or of a failure. Rather, these animals can utilize the ability to lower the set-point of T_b much more than other mammals.

Most flying foxes (Megachiroptera) show normal temperature regulation (Bartholomew et al. 1964, Kulzer 1963 a, 1963 b, 1965). In contradiction to earlier observations, even Microchiroptera (bats) are homeothermic if they are not in their daily sleep (Davis 1970, Henshaw 1970, Kulzer 1967, Kulzer et al. 1970, Lyman 1970, Stones and Wiebers 1965). Some authors have subdivided the Chiroptera into several types depending on their thermoregulatory capacities (Henshaw 1970, McNab 1969, Studier and Wilson 1970), but these can be strongly modified by adaptation (Kulzer et al. 1970).

Brown adipose tissue: The physiology of brown fat is dealt with in several reviews (Boulouard 1970, Smalley and Dryer 1967, Smith and Horwitz 1969). Certain authors have described the distribution of brown fat in mammals (Rowlatt et al. 1971), its annual rhythm of development, and its histology and biochemistry in hibernators (Burlington et al. 1969, Draskoczy and Lyman 1967, Horwitz 1973, Schierer 1956). This organ may be found in all mammals immediately after birth. In hibernators it is well developed, but is lacking in the echidna (Allison and van Twyver 1972) and in birds. It is involved in non-shivering thermogenesis not only in awake animals but also during arousal from hibernation (Hayward 1971, Heldmaier 1969, Jansky 1973, Merker and Wünnenberg 1974) and daily torpor. It also probably is involved in temperature regulation during hibernation itself, and during artificial hypothermia and rewarming (Andjus 1969, Heller and Colliver 1974). Earlier observations, which indicated a depressing effect of brown fat on metabolism (Kayser 1961) could not be confirmed.

Brown fat contains and stores several hormones (androgens, corticosteroids, catecholamines) (Joel 1975, Linck et al. 1973) and it may be able to synthesize steroids. During hibernation, hormones may be released or used up by the organ itself, thus supporting the extremely high metabolism of this tissue (Draskoczy and Lyman 1967, Joel 1965). Arousal is accompanied by further increase of O_2-consumption but a decrease of the Q_{10}. Brown fat contains all of the enzymes which are necessary for breakdown and synthesis of fat and glycogen. The activation of brown fat during arousal takes place by sympathetic control and by the endocrine system. This leads to an explosive lipolysis (Heldmaier 1969, Joel 1965) and a loss of fat from the organ (Burlington et al. 1969). This can be prevented by blocking the adrenergic beta-receptors.

Cold adaptation: After cold adaptation or artificial hypothermia, awake hibernators increase their basal metabolism irrespective of the season (Jansky 1965, Kulzer 1965, Malan and Hildwein 1965, Mletzko and Raths 1972 a). Thermal conductance may decrease (Pohl 1965 b). Several species do not require cold adaptation for the onset of hibernation, but certain other species hibernate only after a period of cold adaptation of 1—10 days or even more, depending on the season (Kayser 1961, Senturia and Johansson 1972). In bats, hibernation and daily sleep lethargy are distinguished from each other by the added cold adaptation. After adaption to room temperature during winter, bats cannot arouse from deep lethargy at low T_a, but they can arouse in summer after a cold adaption lasting about three weeks (Henshaw 1968, Pohl 1961, Rauch and Beatty 1975). In Australian species of bats, the ability to hibernate and to arouse at low T_a developed after cold adaptation (Kulzer et al. 1970). Obviously hibernation in these mammals depends on the formation of brown fat and the increase in non-shivering thermogenesis (Heldmaier 1969, Pohl 1961). Probably for the same reason, the dormouse requires a cold adaptation to enter hibernation, but not for a period of aestivation (Kayser 1961). It is of interest that the T_b of the poorwill during lethargy falls, as it adapts to cold.

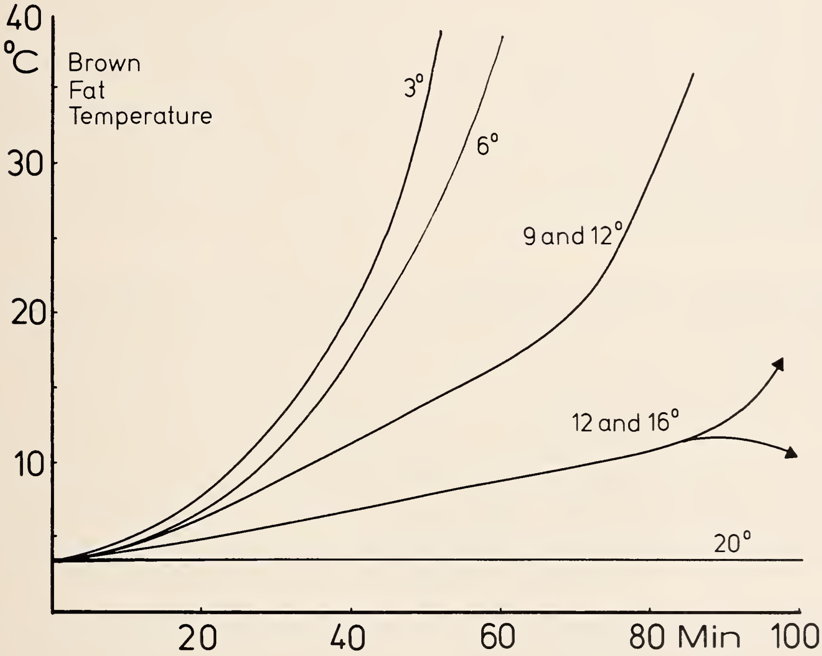

Fig. 27: Rates of body temperature increase in *Myotis lucifugus* acclimatized to different air temperatures. Temperatures taken in interscapular brown fat. The rapid phase of arousal was delayed or absent in bats acclimatized to intermediate temperatures. Rapid and slow phases were absent in bats acclimatized to 20° C. From Henshaw (1970).

Ambient temperature: Aestivation may even occur at T_a between 27° and 33 ° C (Bartholomew and Hudson 1960) and hibernation between −5° and 25° C (Eisentraut 1956, Herter 1956), so that there is actually no range in T_a, in which torpor would be impossible. However, a particular T_a may play the role of a cue. For example, several tropical and subtropical bats do not enter lethargy if T_a is lower than 17° C. In these bats, T_b not lower than 17° C is a pre-condition for spontaneous arousal at low T_a (Kulzer 1965). Limits of T_a between 15° and 25 ° C were also found for torpor in various other species (Bartholomew et al. 1970, Scholl 1974). The European hedgehog and hamster become lethargic easier at T_a 10° C than at 2° C or even than at −8° C (Bartos 1960). Generally, a temperature preference exists for the onset of lethargy, even a preference for a special microclimate (Bats: Davis 1970). If readiness for hibernation is present (Herter 1956) the thermal preferendum may be adjusted to a low T_a. Accordingly, the depth of the sleeping nest below the ground, may be related to the seasonal T_a (Eisentraut 1956, Herter 1956).

Poikilothermy during torpor: In different species hibernation begins with marked periodical fluctuations of T_b in a circadian rhythm (Strum-

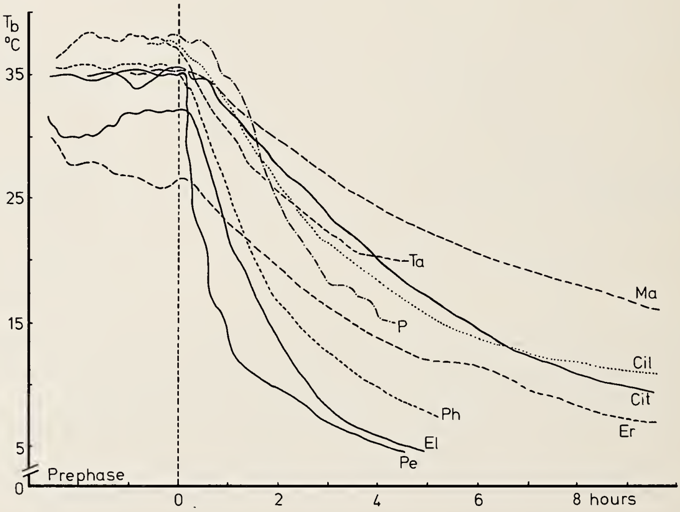

Fig. 28: Drop of body temperature during entrance into hibernation. Pe = *Perognathus longimembris*, 8 g, T_a 3° C (Bartholomew and Cade 1957), P = *Perognathus hispidus*, 40 g, T_a 11° C (Wang and Hudson 1970), Ta = *Tamias striatus*, 95 g, T_a 10° C (Wang and Hudson 1971), El = *Eliomys quercinus*, 190 g, T_a 4° C (Pajunen 1970), Cil = *Citellus lateralis*, 190 g, T_a 6° C (Twente and Twente 1965), Cit = *Citellus tridecemlineatus*, 200 g, T_a 4° C (Lyman and O'Brien 1960), Er = *Erinaceus europaeus*, 680 g, T_a 4° C (Suomalainen and Saarikoski 1970), Ma = *Marmota monax*, 1500 g, T_a 10° C (Lyman 1958), Ph = *Phalaenoptilus nuttalli*, 43 g, T_a 2°—6° C (Howell and Bartholomew 1959).

wasser et al. 1964) or in shorter periods (Weigold 1973) called "test drops" (Strumwasser 1960). The decrease of the set-point of T_b in mammals is accompanied by vasodilation (Chew et al. 1967, Strumwasser 1969 a) but in birds probably only by a reduction of thermogenesis (MacMillen and Trost 1967 a). The fall in T_b is controlled: It proceeds more slowly than in mammals with hypothalamic lesions (Koski and Conover 1971). The curve is S-shaped (birds: Bartholomew et al. 1957) and frequently wavelike. This is correlated with the temporary phases of shivering, tachycardia and a raised O_2-consumption (Hudson 1969, Lyman 1965, Sturmwasser 1960, Weigold 1973). By applying the Newtonian law of cooling and van't Hoff's law (of the steady state) during torpor, smaller animals owing to their smaller heat capacity and greater surface area cool more rapidly than large ones (Hammel et al. 1968, Lasiewski et al. 1967, Wang 1973). The problem has been discussed by many authors (Kayser 1964 a, Morrison 1960, South and House 1967). This discussion finally led to a mathematical model of cooling for the marmot (Luecke et al. 1971).

The so-called "second homeothermic state": In spite of the "controlled" decrease in T_b at the onset of hibernation, during torpor the animals are poikilothermic. When the minimal T_b falls to just above 0° C, a standard of the depth of hibernation is established. This was realized in principle by Wyss (1932) and described as a "second homeothermy". This state occurs also in lethargy during sleep (diurnal torpor) of cangaroo rats (Mullen 1971) and white-footed mice (Hill 1975) as well as during nocturnal torpor in hummingbirds (Wolf and Hainsworth 1972). This regulation takes place by means of the well known chemical and physical interactions (Davis 1970, Henshaw 1968, 1970, Kayser 1961).

An extreme decrease in T_a however induces arousal. In rare cases the animals become supercooled to $-5°$ C. At this point, they loose the ability of active rewarming but may survive after rewarming passively (Dyer 1968, Mayer W. V. 1960). Although most authors agree in the existence of a hibernation-homeothermy, recently some objections were made (Hammel 1967, Hammel et al. 1968): The hibernatory regulation of T_b would be a rough reflex mechanism only, in the sense of "partial arousal".

The set-point during torpor is specific for each species. In most cases it lies between T_b 8° and 1° C. In addition, temperature adaptation and nutrition may play a role (Bartholomew and Trost 1970, Peiponen 1966), so that the set-point, to a certain degree, is adjustable (Heller 1974, Heller and Colliver 1974, Wang 1973). One can suppose that the attained T_b is identical with the temperature level necessary for active rewarming or maintenance of electrolyte balance (Hudson and Eller 1974). In "classical" hibernators this temperature lies between 0.5° and 5° C. However, in many mammalian species it is between 15° and 20° C, (in bears between 31.2°

and 34° C), and in birds between 1° and 28.5° C (Chew et al. 1967, Hock 1960, Hudson 1969, MacMillen 1965, Raths 1975).

Arousal: Arousal from torpor at low T_a involves an enormous thermoregulatory stress. Activation of the sympathetic system leads immediately to a doubling of the cardiac frequency, to an abdominal vasoconstriction and to a mobilization of brown fat (bats: Kallen 1960, Kulzer 1967, Mejsnar and Jansky 1970, Rauch 1973). However, anatomically, the sympathetic system in bats shows no special features (Webber and Kallen 1968). Increasing blood flow to the brown fat is probably the primary cause of the differential regional blood distribution between the anterior and posterior parts of the body, and the faster warming of the anterior part compared to the posterior (Rauch 1973). In arousing chipmunks (Wang and Hudson 1971) and in several aestivators (Bartholomew and Hudson 1960, Hudson et al. 1972), the anterior-posterior temperature gradient is absent.

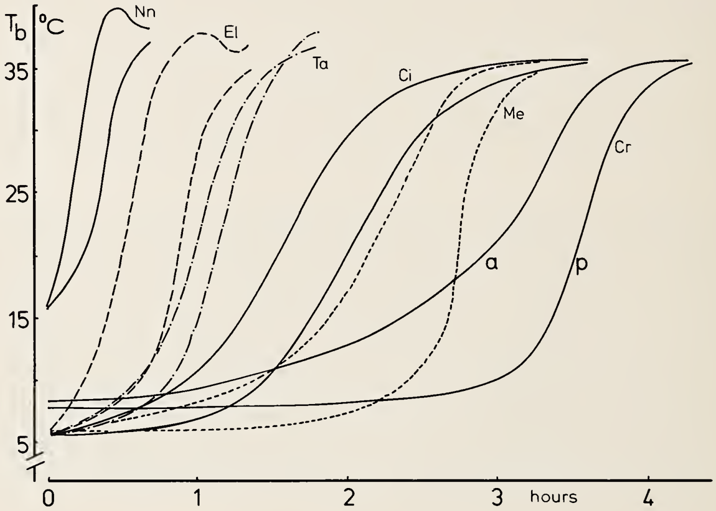

Fig. 29: Increase of T_b during arousal from hibernation; anterior (a) T_b of head or chest, posterior (p) rectal temperature. T_a (except in the bat *Nyctalus*) between 3.5°—6° C. Nn = *Nyctalus noctula* (Kulzer 1969), El = *Eliomys quercinus* (Ambid 1971), Ta = *Tamias striatus* (Wang and Hudson 1971), Me = *Mesocricetus auratus* (Lyman 1948), Ci = *Citellus undulatus* (Feist and Galster 1974), Cr = *Cricetus cricetus* (Raths unpubl.).

The speedy increase in metabolism during arousal is only possible by a general activation of the endocrine system and by the removal of the inhibition of many enzymes (Zimny and Clement 1961). In this manner, oxydative metabolism increases (Hammel et al. 1968, Wang and Hudson 1971), but simultaneously there is a burst of glycolysis (Ferdmann and

Feinschmidt 1934, Galster and Morrison 1975, Olsson 1972) and a partial uncoupling of oxydative phosphorylation (Roberts and Chaffee 1972). The last phase of arousal is marked by a decreasing lipolysis and an increasing lipogenesis as well as the rebuilding of the brown fat reserves (Ambid 1971, Joel 1965). The energy for this is derived from carbohydrates. The mitochondria of different organs swell (Törö and Viragh 1966).

The first phase of arousal (to about 15° C T_b) is marked by an increasing muscle tone, but especially by non-shivering thermogenesis in the brown fat and other organs. The second phase is characterized by an enormous shivering. The two mechanisms of thermogenesis can be independently suppressed by sympatholytic agents, and by curare, respectively (Hayward 1971, Heldmaier 1969, Jansky 1973, Joel 1965, Lyman 1965, Mejsnar and Jansky 1970, Smith and Horwitz 1969). The rewarming process lasts 1—4 hours, but it also depends upon the T_a and the initial T_b. In the echidna, which lacks brown fat, arousal lasts about 20 hours (Allison and Twyver 1972). Bats possess very different thermoregulatory capacities during arousal (Kulzer et al. 1970). Generally, the time of rewarming in smaller species of mammals and birds is shorter than in larger animals (Kulzer 1965, Pearson 1960).

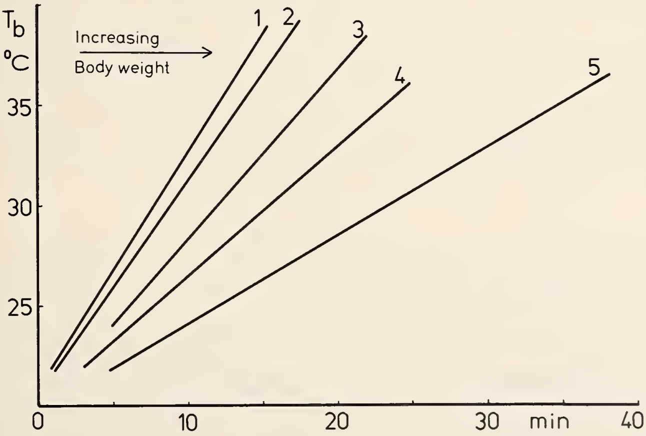

Fig. 30: The increase in body temperature during arousal from torpor in birds (T_a 21°—23° C). Adapted from Lasiewski et al. (1967). 1 = *Archilochus alexandri* (4 g), 2 = *Eugenes fulgens* (6,8 g), 3 = *Lampornis clemenciae* (8,5 g), 4 = *Patagona gigas* (21 g), 5 = *Phalaenoptilus nuttallii* (40 g).

Thermoreceptors: It has been known for a long time that hibernators during torpor react with autonomic reflexes to cold. As in other mammals, these reflexes are elicited especially by stimulation of the head and less

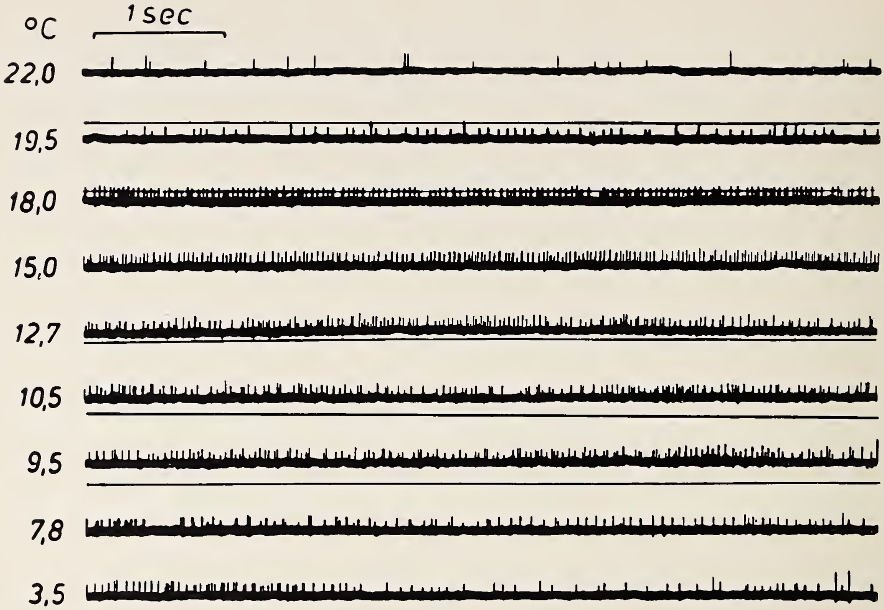

Fig. 31: "Stationary" activity of few cutaneous Aδ-cold fibres of the intraorbital branch of trigeminal nerve at cutaneous temperatures between 22° and 3.5° C (*Cricetus cricetus*). From Raths (1967).

by stimulation of the trunk (Lyman and O'Brien 1974, Raths and Hensel 1967). In hibernators, the face is of high thermoregulatory importance (Mletzko and Raths 1972 b). Its thermoreceptors exhibit activity at 0° C or even lower. Equally from diencephalic thermo-receptive structures (as in other mammals) reflexes can be elicited by cooling or warming (Heller and Hammel 1972, Heller et al. 1974, Malan 1969, Mills et al. 1974, South et al. 1975, Williams and Heath 1971), even in torpor at extremly low T_b. Microelectrode recordings from central structures at low T_b are lacking (Boulant and Bignall 1973). — Lethargy cannot be induced by central thermal stimulation. However, central warming in arousing ground squirrels and marmots, immediately leads to a resumption of torpor, to bradycardia, and even to behavioural defense reactions (Heller and Hammel 1972). These reactions generally suggest the existence of a hibernation set-point in T_b. In contrast, central cooling leads to increased thermogenesis or to arousal, especially at lower T_a (Heller and Hammel 1972, Heller and Colliver 1974). Even here an interaction between dominant central and peripheral thermoreceptors is apparent. Curiously in marmots, effective thermoregulation was not apparent until three or four days of continuous hibernation had elapsed (South et al. 1975).

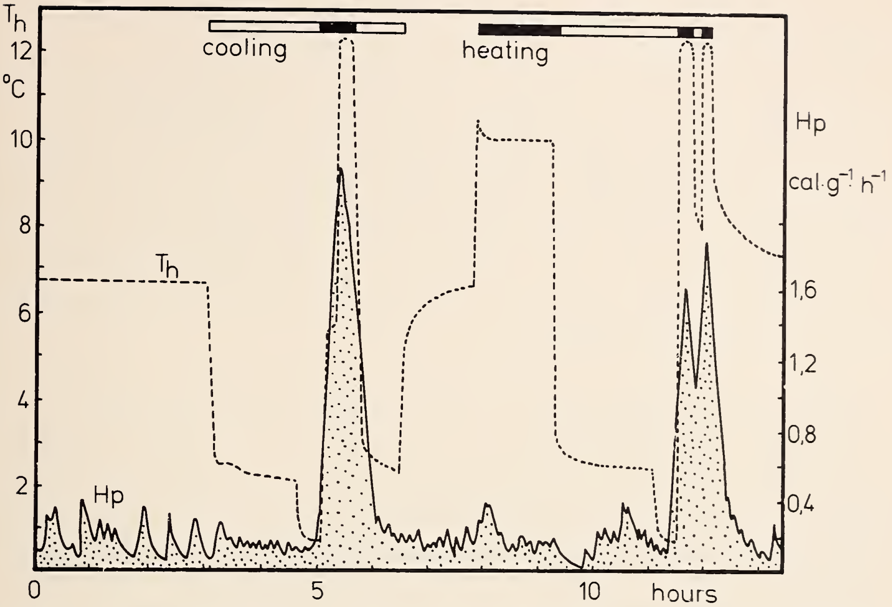

Fig. 32: Arousals induced by cooling and reversed by heating the hypothalamus in deep hibernation. T_a (Calorimeter wall temp.) 6° C; adapted from Heller and Hammel (1972). T_h = hypothalamic temperature, Hp = heat production.

Central regulation of hibernation: Destruction of the hypothalamus in awake animals interferes with thermoregulation and with the readiness for hibernation (Malan 1969, Raths and Perlick 1953) and so produces an apathy or a form of "drowsiness", but no hibernation (Satinoff 1970). Ventromedial and other hypothalamic lesions are compatible with hibernation and arousal (Raths and Bohn 1975, Mrosovsky 1975). However, lesion of the rostral hypothalamus during hibernation makes arousal impossible or inhibits rewarming (Kluger and Heath 1971, Satinoff 1970). Destructions in the limbic system and hypothalamus inhibit the decrease in T_b during entrance into hibernation, while several other hypothalamic lesions accelerate it (Koski and Conover 1971, Weidler et al. 1974). Thus the limbic system, including the hypothalamus, seems to be involved in regulation of hibernation. Numerous investigations of EEG have shown that the spontaneous electrical activity of the brain decreases with decreasing T_b in an orderly sequence from neocortex, medial thalamus, thalamus, olfactory bulb and finally hippocampus and related limbic structures and the mesencephalic reticular formation (Mihailovic 1972). Arousal proceeds with a faster reappearance of electrical activity in the reverse sequence (Allison and Twyver 1972, Kayser 1961, Kayser and Malan 1963, Raths 1958, Shtark 1965). Thus continuous activity of the neocortex is extinguished and appears again between 20° and 15° C T_b (exceptions: Strumwasser 1959 b, 1960). During deep hibernation (brain temperature 7°—8° C), prominent features of the electrical activity in the marmot (Mihailovic 1972) were occasional spindels originating from the frontal cortex and spikes from occipital cortex, with an associated background activity in the hypothalamus and the mesencephalic reticular formation (MRF). Increased activity in the hypothalamus and MRF were observed before the first detectable rise in brain temperature at the beginning of arousal. The idea of a limbic and possibly hypothalamic control of hibernation and arousal is partially based on EEG-investigations (Heller and Colliver 1974, Heller et al. 1974, Luecke et al. 1971, South et al. 1972 b).

Mammals assist temperature regulation by instinctive and learned behaviour. Hypothermic rats even learn to switch on a heater. Hibernators in artificial hypothermia however are unable to do this. By contrast, electrical self-stimulation experiments are possible in *Citellus* at 24,7° C T_b (Mrosovsky 1966). During hibernation, the instinctive and learned performances of several species are quite good. Marmots correct their resting posture depending on T_a, and in contrast to European hamsters, hedgehogs *(Hemiechinus)* and bats, they do not lose their tameness (Eisentraut 1956). *Citellus* at 1° C T_b learn not to wake even after intensive mechanical stimulation (Pengelley and Fisher 1968). After arousal they even remember previously fixed engrammes (Mihailovic et al. 1968).

Luecke and South (1972) have recently discussed the problems of thermoregulation during hibernation proposing a model from Hammel (1967). The physiological fine structures are hi-Q_{10} and lo-Q_{10} neurons in the hypothalamus. They synapse with motor neurons which may be facilitated or inhibited in order to generate a thermoregulatory response (vasoconstriction, shivering, panting). Axons of the peripheral warm and cold receptors synapse also with the sensory neurons. A change in temperature causes an increase in the firing rate of either the hi- or lo-Q_{10} receptors. Entry into hibernation occurs by an active and powerful synaptic inhibition of the lo-Q_{10} sensors. The suppression of their activity begins to fail when low temperatures near freezing are approached. Then their increased firing rate would lead to some degree of thermogenesis and to a rise in brain temperature, which in turn would permit again an inhibition. A low temperature set-point could be created, variable on both a long and a short time basis. Thus, two stages of entry into hibernation are proposed: a resistance phase, consisting of cyclical interactions between excitatory and inhibitory mechanisms, and a compliance phase during which the inhibitory function is imperatively imposed. The initiation of the latter is signalled by peculiar outbursts of electrical activity of the limbic system including hippocampus and preoptic area.

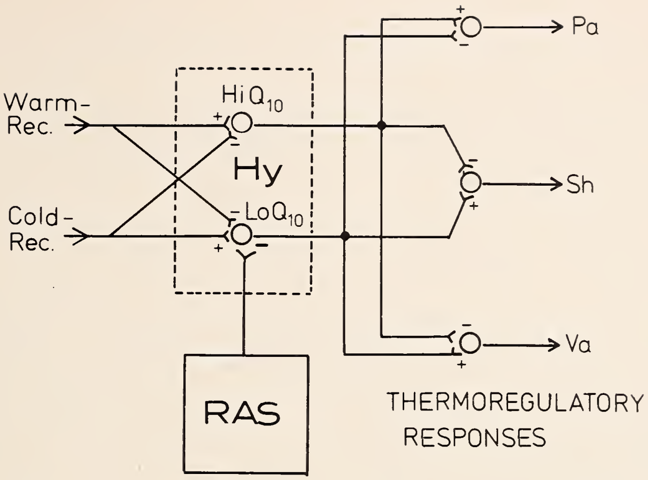

Fig. 33: Proposed model for thermoregulatory system for hibernators (adapted from Luecke and South 1972). Neurons in the hypothalamus (Hy) having firing rates which are strongly temperature dependent ($Q_{10} \gg 1$) over the range of normal T_b (= Hi Q_{10} — sensory neurons). The Lo Q_{10} — sensory neurons are assumed to have firing rates over the range of T_b; they are not strongly temperature dependent. Both synapse with and facilitate or inhibit the neurons which activate regulatory responses. Hammel (1967) suggests that the cold sensory neurons could be suppressed during hibernation by an inhibitory signal from the reticular activating system (RAS) which would remove central control over T_b.

Throughout the period of deep hibernation active thermoregulatory control is present (defense against cold). The subcortical structures remain in active control. Their electrical activity is characterized by intermittent localized bursts or spikes. The nature of the stimuli responsible for spontaneous arousal is still moot. No specific electrical activity in the brain has been found which induces the arousal process; once initiated, it is coordinated by the limbic system and may be expressed as a generalized sympathetic discharge (South et al. 1972 a).

Summary: Beside the physical, chemical and behavioural temperature regulation, hibernators possess the ability to voluntarily lower the T_b. Brown fat plays a role as a source of thermogenesis in awake mammals, during arousal and probably during torpor itself. Cold adaptation raises the basal metabolism and simultaneously, in several species, increases the readiness for hibernation. Torpor may start at low and at high T_a. The fall of T_b is controlled. During deep torpor, temperature regulation is possible. The peripheral and central thermoreceptors are still excitable at 0° C. In several species, central regulation during hibernation originates mainly from the mesencephalon, while in others it originates from the diencephalon and from the limbic system.

X. Function of Sense Organs

Because of the high resistance of nerve fibres to cold, the conduction of sensory impulses at low T_b is readily possible (Boldt and Biewald 1971, Kehl and Morrison 1960, Raths and Bohn 1975). However during torpor, the sense organs presumably have only an arousal function exciting the reticular activating system (Beckman et al. 1976). For this purpose, it may be sufficient if the receptors become excited at low T_b and if the afferent impulses induce a reflex arousal via the brain-stem. The effectiveness of tactile, thermal and pain stimuli has been known for some time, and can be confirmed by the recording of action potentials in European hamsters (Raths and Hensel 1967). The thermal dependence of the discharge frequency of mechanoreceptors is remarkably low (Boldt and Biewald 1971). The effectiveness of acoustic signals in ground squirrels and in marmots is evident from their reflex actions (Strumwasser 1960) and evoked cortex potentials (Kayser 1961). Deafness facilitates or deepens the torpor in chipmunks (Wang and Hudson 1971). Probably there are differences between species, because bats seem to be deaf below 12° C T_b, but the midbrain "sonar center" is excitable even at 5° C T_b (Howell et al. 1975). In the awakening European hamster, the eye first reacts electrically above 10° C T_b, the pupillary reflex first functions at 15° C and the normal electroretinogram appears at 25° C (Biewald 1967 b). If hibernators are not aroused by noise (Folk 1960) or by rotation, and if no cardiac reflexes and no inhibition of shivering (Raths 1958) can be induced at low T_b, it does

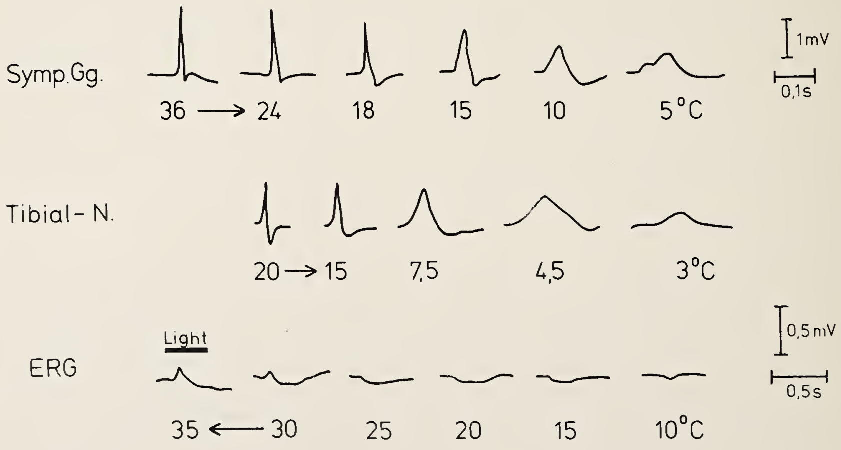

Fig. 34: Excitability in hibernators. Effect of temperature on the postganglionic action potential of an isolated sympathetic ganglion of *Erinaceus europaeus* (from Saarikoski 1969), on the action potential of the isolated tibial nerve of *Mesocricetus auratus* (from Chatfield et al. 1948) and on the electroretinogram of arousing *Cricetus cricetus* (from Biewald 1967).

not follow that the sense organs are not functioning, because integrative attainments of the central nervous system may prevent this.

Summary: Some of the sense organs, especially receptors in the skin and the auditory sense, are functioning during hibernation and therefore are qualified to induce arousal.

XI. Biological Rhythms

Annual cycle: Mechanisms by which hibernators synchronize the timing of their behaviour with the changing seasons are still poorly understood. In a recent study (Pengelley and Asmundson 1972) which elucidate the problem, the interrelationship of body weight and hibernation periods was investigated in *Citellus lateralis* for nearly four years. There seems good reason to suppose that the underlying mechanism of the animal's ability to synchronize its behaviour with the changing environmental conditions is an endogenous circannual rhythm. This hypothesis was confirmed by Heller and Poulson (1970), who kept ground squirrels under constant laboratory conditions for 33 months. They were able to measure 17 free-running circannual periods with a mean of 51 weeks (358 days). All data fit the criteria for a circannual rhythm with the exception that there is as yet no exact knowledge of the "Zeitgebers". Temperature and light have been implicated as potential "Zeitgebers" (Drescher 1967, Pengelley and Asmundsen 1970). Within the genus *Citellus* there are species, in which the photoperiod plays little if any role (Pengelley 1967), while in other species and in the golden hamster the readiness to hibernate is stimulated by short daylength. A short daylength also stimulates aestivation (Morris and Morrison 1964). Total darkness (DD-conditions) is especially effective on

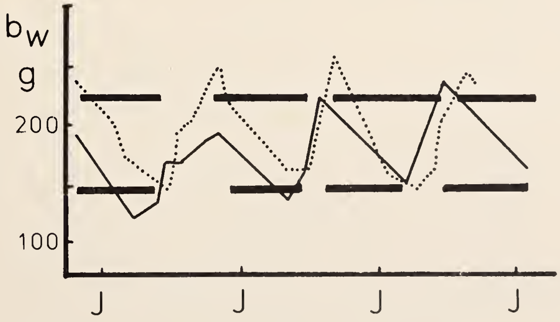

Fig. 35: Interrelationship of body weight (b_w) in g and whole hibernation periods (black bars) of two animals (*Citellus lateralis*) for nearly four years. Upper animal (T_a 12° C), lower animal (T_a 3° C); both with artificial photoperiod of 12 hours. Adapted from Pengelley and Asmundson (1972). J = January.

the lethargy of birds (Bartholomew et al. 1957, Dawson and Hudson 1970, Lasiewski 1964) but not on the hibernation of the dormouse (Kayser and Hildwein 1969). In these animals continuous light (LL) and long-day conditions inhibit torpor (Morris and Morrison 1964). Induction of torpor within certain ranges of T_a, by water deprivation and by food shortage has been discussed above. If the endogenous readiness is high, such signals are probably unnecessary (Yousef and Bradley 1971).

The onset of hibernation is introduced by a preparatory behaviour (preparation of winter quarters, hoarding of food, hyperphagia, migration in bats). Thus, hibernation and aestivation can be interpreted as instinctive behaviour (consummatory behaviour) (Herter 1956). Like instincts, the hibernation patterns are hereditary for species, races and tribes (Chaffee 1966, Pajunen 1974). They are not lost by geographical transposition (Hildwein 1970) or by reversal of the annual light cycle (Morris and Morrison 1964). The hibernation rhythm therefore is endogenous (Heller and Poulson 1970, Kayser and Heusner 1967, MacMillen and Trost 1967 b, Strumwasser et al. 1970). However, ecological factors play a role in initiating the hibernation season (Pengelley and Asmundson 1975, Yousef and Bradley 1971). According to various authors, learning processes are involved in the onset of hibernation (Kalabukhov 1956) similar to the conditioning to low oxygen pressure hypothermia (Bullard et al. 1960).

Circadian rhythms: The circadian rhythms of T_b, motor activity and basal metabolic rate, are endogenous. The length of the period is about 24 hours, but it is prolonged in the dormouse by a cold environment (Pohl 1965 a). The same is true for the European hamster during autumn (Mletzko and Raths 1972). The active phase (α-phase) is generally shortened because of the increasing necessity for sleep from summer to autumn (Kayser and Hildwein 1969). In Madagassian hedgehogs (Tenrecidae) cold changes the length of the α-phase (Herter 1962, 1964 a).

Hibernation and daily torpor begin during the inactive (resting) phase (ϱ-phase) (Dawson and Hudson 1970, Pohl 1961, 1964, Wyss 1932). In several species, circadian changes in T_b precede the torpor (Strumwasser 1960, Strumwasser et al. 1964), and even during hibernation, circadian fluctuations of T_b, O_2-consumption, respiration and cardiac frequency are observed, but disappear at extremely low T_b (Kayser and Heusner 1967, Menaker 1959, 1961, Pohl 1961, 1964, 1965 a). The circadian oscillations of adrenaline and noradrenaline concentrations in the adrenals and in the spleen of hibernating golden hamsters are greater than in awake animals (Lew and Quay 1973). In the dormouse, even circadian fluctuations of the enzymatic activities of gut, liver and pancreas persist during hibernation (Sauerbier 1976).

Arousal from lethargy usually takes place during the "Zeitgeber"-dependent α-phase of the normothermic state (Folk 1960, Johansen and

Krog 1959, Strumwasser 1960, Suomalainen and Saarikoski 1970). Some of these findings may be accidental, because free running circadian rhythms may be somewhat longer or shorter than 24 hours. Consequently, during torpor with no "Zeitgeber", there is after several days a marked phase shift or even a reversal of the daily light-dark cycle. Therefore, light-active hibernators might arouse during the night and dark-active animals during the day (Mletzko and Raths 1972 a).

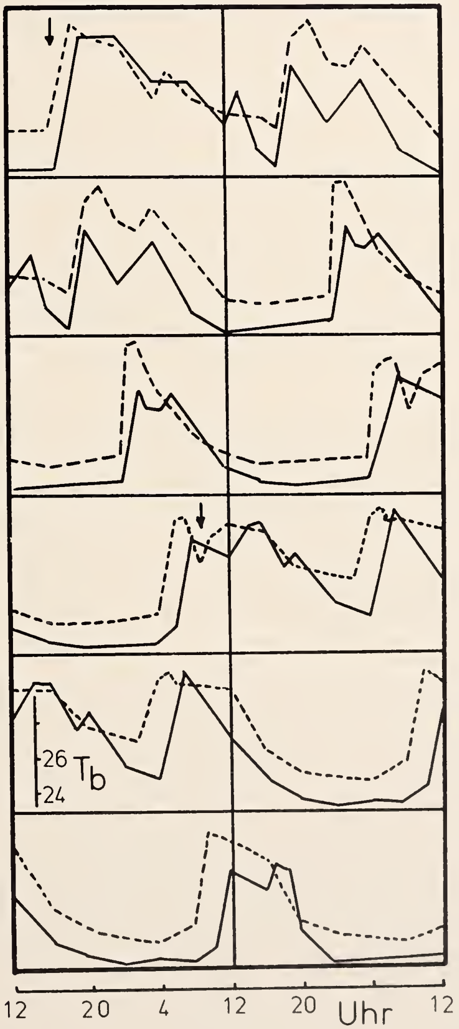

Fig. 36: Circadian rhythm of body temperature in two tenrecs *(Echinops telfairi)* under constant light conditions (LL); → = food was offered. From Scholl (1974).

Lethargy and normothermic sleep: The change between asleep and awake is one of the best known circadian rhythms. Every kind of lethargy develops from normal sleep. From the muscle tone in the neck as well as from the EEG, it can be ascertained that hibernation begins during the slow wave sleep (Satinoff 1970, South et al. 1969, Wang and Hudson 1971). However, in marmots at T_b of 20° C an alternating change from slow wave to REM-sleep can be proved (South et al. 1969).

According to the monoamine theory of Jouvet (1972) the rhythm between asleep and awake may be controlled by biogenic amines which are released by and act on the central nervous system. But according to Myers and Buckman (1972) these substances together with Ca also play a role in temperature regulation. Jouvet states that the chemical reactions controlling the sleep and waking state, originate from the mesencephalon and from the pons. Slow wave sleep is initiated by serotonin moving from the anterior raphe nuclei of the pons to the pre-optic area and by inhibition of the alerting system in the tegmentum and the substantia nigra. REM-sleep originates from the caudal serotoninergic raphe nuclei and includes the noradrenaline system of the caudal pontine locus coeruleus. The system of alertness is partially noradrenergic (anterior locus coeruleus) and partially dopaminergic (substantia nigra).

The results from the injection of chemicals into the diencephalon of hibernators like those in other mammals (outline: Hensel et al. 1973) are contradictory. Ca induces preparatory and prehibernatory behaviour and hypothermia but no real hibernation (Hanegan and Williams 1975, Myers and Buckman 1972). Adrenaline and carbachol decrease (Jacobs et al. 1971, Mrosovsky 1974 b), whereas noradrenaline decreases or increases somewhat the T_b and serotonin raises it (Beckman and Satinoff 1972, Mrosovsky 1974). However, hibernation does not develop.

The concentration of central transmitters was studied in part histochemically (fluorescence), in part chemically. The dopamine system (behaviour-wakefulness) is probably inactive during hibernation (Barry 1971). Because noradrenaline may play a role in the system of wakefulness as well as in the REM-sleep, interpretations are very difficult. Most results suggest a decrease in brain noradrenaline before the torpor begins or a blocking of its synthesis by low T_b (Feist and Galster 1974). The inhibition of the central noradrenergic neurons probably is the first step in the beginning of hibernation (Draskoczy and Lyman 1967), whereas arousal is accompanied by an increase of hypothalamic catecholamines (Feist and Galster 1974). Therefore, noradrenaline seems to be a "thermogenic mediator".

The serotonin system (slow wave sleep) is active during hibernation and aestivation (Barry 1971). The serotonin concentration of the hippocampus and hypothalamus is highest during prehibernation but diminishes after onset or during continuous lethargy (Jansky and Novotna 1974, Kudrjavtseva 1973, Spafford and Pengelley 1971). Low values may occur at low T_a during wakefulness or during arousal processes (Feist and Galster 1974, Jansky and Novotna 1974, Kudrjavtseva 1973). The significance of the serotonin system lies in the fact that with serotonin inhibitors, hibernation can be prevented (Constantinidis et al. 1970, Jaeger 1971, Spafford and Pengelley 1971), as it can be by destruction of the median raphe nuclei. On the other hand, reserpine and serotonin lengthen the arousal from hibernation (Faure 1973, Popova 1975). According to these findings serotonin is related to the slow wave sleep, and acts in hibernation as a "cooling transmitter".

It is still uncertain if some other chemical substances trigger the onset of hibernation. This is suggested by the induction of a hypothermic sleep in the cat and in the dog by the injection of an extract from the brains of various hibernating mammals. Similar results were obtained from rats after using the brain of aestivating lungfishes *(Protopterus aethiopicus:* Swan et al. 1969). Perhaps in these actions, gamma-amino butyric acid plays a role. Its concentration in the brain increases during hibernation (Kristoffersson and Broberg 1970, Nelson et al. 1973). The existence of hibernation inducing substances in the lymphatic tissues and in brown fat (Kayser 1961) is very dubious.

Recently in *Citellus,* even in infants, the torporous state could be induced by infusion of blood, preserved blood, serum, serum-dialysate and washed blood cells from hibernating ground squirrels and marmots. However, the triggering substance is not formed in awake animals during cold adaptation, but only during torpor itself (Dawe and Spurrier 1972, 1974). This would agree with the concept of Hess: "Sleep produces sleep". The theory suggests an interaction between trigger and inhibitory molecules (Dawe and Spurrier 1974).

Triggering of arousal: The length of a hibernation bout lasts from a few days to several weeks. A bout lasts longer, the lower the T_b (Jaeger 1974, Kristoffersson and Soivio 1964, 1967, Lyman 1965, Petrovic 1960). The same is true for the daily sleep lethargy. Perhaps the "torpor-quantity" (duration x T_b), analogous to the quantitiy of sleep, is a constant factor. Because of the effectiveness of van't Hoff's law and the fact that the kidneys do not function efficiently, this quantity is proportional to the quantity of metabolites which are formed during torpor. Such alterations in the "milieu interieur" have already been mentioned. They consist of a rise of Ca, Mg and acids in blood, a decrease of blood sugar, a fall in levels of energy-rich phosphates and vitamins, hypoxia, urea accumulation, alterations in the hormone levels and enzymatic activity, formation of creatinine (Lis et al. 1972) and production of adenyl-cyclase and the formation of cyclic AMP (Twente et al. 1970). This "metabolism hypothesis" fits well with the fact

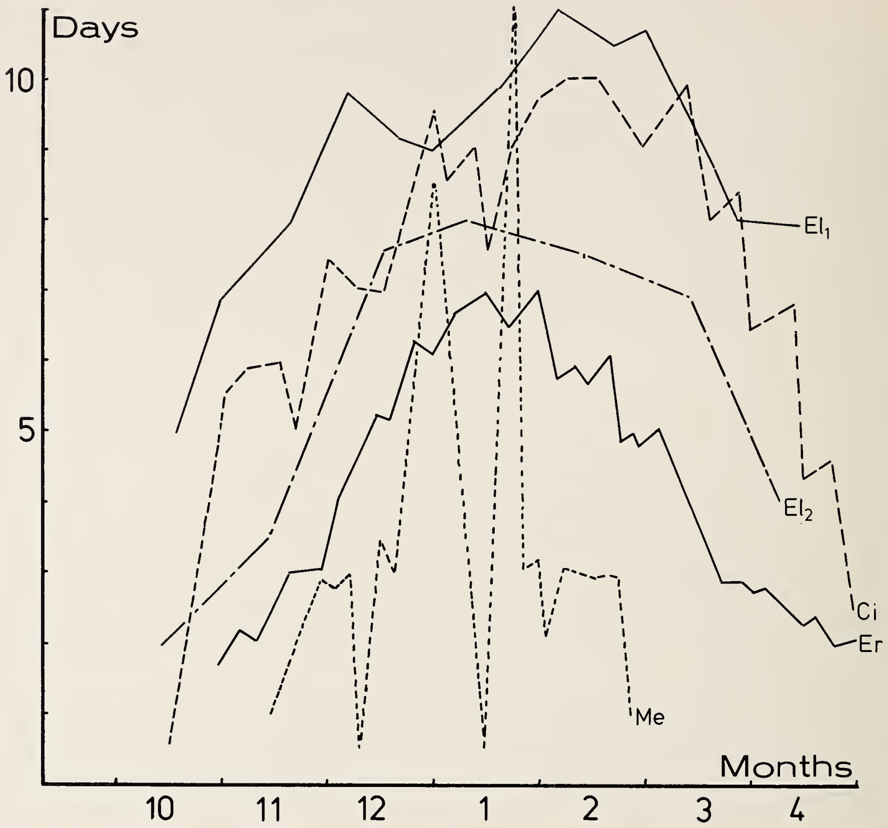

Fig. 37: Duration of hibernation bouts with respect to the annual season. Ci = *Citellus lateralis*, average curve (Strumwasser et al. 1964), El_1 = *Eliomys quercinus*, average curve (Pajunen 1970), El_2 = *Eliomys quercinus* (Gabe et al. 1964), Er = *Erinaceus europaeus*, average curve (Kristoffersson and Soivio 1967), Me = *Mesocricetus auratus* (Pohl 1961).

that an increasing sensitivity to arousal is correlated with the progressive lengthening of the bout. This is true for the excitation of receptors as well as for excitation by the injection of salt solutions, drugs or hormones (Twente and Twente 1968). Inhibition of periodical arousal, perhaps by destruction of the pre-optic area, leads within ten days of hibernation to death (Satinoff 1970). However Satinoff concludes from that, that "arousals are programmed by the initial amount and rate of dissipation of a central inhibitory transmitter" and not by an accumulation of metabolites.

The increasing length of hibernation bouts from autumn to midwinter and the decreasing length in spring at constant T_a conditions (Jaeger 1974, Kristoffersson and Soivio 1964, Twente and Twente 1967) cannot be determined by T_b alone. Here the seasonal alterations in hormonal balance could play a role (Pengelley and Asmundson 1975). As a third factor, instinctive and learned behaviour could be important because the length of the torpor bouts increases with the amount of stored or consumed food (Mrosovsky and Barnes 1974).

The earlier concept that the filling of the bladder could be the real stimulus for arousal, surely is not true. A new attempt to interprete the arousal timing by reflexes was undertaken by Lyman and O'Brien (1969). It is known (Lyman 1965, Weigold 1973) that the first reaction to a stimulus for arousal consists of a burst of muscle action potentials, followed by a reflex inspiration and cardioacceleration. The same reactions were obtained after infusion of acids, bases or acetylcholine via a chronic cannulation of the aorta. The reaction of muscles is greater, the more T_b decreases. Lyman could show by combination of different methods (using hibernating spinal preparations of *Citellus,* sectioned at C_1), including blocking with hexamethonium and curare, destruction of the spinal cord, and thermal stimulation of pain receptors in the back, that the reflex reaction of muscles was increased not only by a rise in muscle sensitivity (cold denervation: Moravec et al. 1973), but also that the reflex is elicited by stimulation of (unknown) receptors via the changed "milieu interieur". The excitation of receptors at very low T_b is possible in hibernators.

Summary: The endogenous circadian and annual rhythms of the different lethargic conditions are synchronized with the daily and annual cycles of the earth. However, knowledge about the interaction between endogenous and exogenous factors is almost totally lacking. It is possible that different timing mechanisms are involved in the daily and seasonal torpor. The lethargic state probably originates from slow wave sleep, in the course of which the serotonin system of the brain stem is of significance. Spontaneous arousal results from a reflex awakening effect which is initiated by the continuously changing "milieu interieur" activating unknown receptors.

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We used about 1200 references for this review and we are sorry that only a small selection of them could be accepted for the reference list.

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