

A Study of the Mechanism on Hibernation*

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The present study was performed in order to test the effects of diphenylhydantoin (DPH) and two central nervous system (CNS) stimulants, intermittent light stimulation (ILS) and pentylenetetrazol (Metrazol) on body temperature (Tb) during cold exposure in the bat. DHP delayed the onset of entry into hibernation in both the oriental discoloured bats and the little brown bats and formed long and prominent plateaus that were not found in the normal and the controls. The responses of body temperature to the ILS were sensitive and the body temperature fell dramatically in the big brown bats. Metrazol effects on body temperature were obvious but seemed dose-dependent.

The experimental results further support the hypothesis that hibernation is an epileptic fit as suggested by several researchers.

All hibernators can live in cold environments for many weeks, keep a high body temperature and remain active. This is because they are really warm-blooded animals. However, among warm-blooded animals the deep hibernators such as bats are able to shut off their body heat-producing mechanisms and lower their body temperature and yet survive long winter months without eating any food at all. Koski (1968) has reported that in bats, the posterior hypothalamus functions to maintain a high body temperature in the cold. He has found that the normal little brown bat

(*Myotis lucifugus*) increased its heart rate and maintained a high body temperature in the cold for 10 hours before entering hibernation. But in the animals lesioned in the posterior hypothalamus, the heart rate did not increase and the rate of the body temperature decline was faster than that of the normal control bats. This suggests that the posterior hypothalamus is closely related to the maintenance of body temperature. The next experiments were performed by Gerhardt and Koski (1973) by means of electroencephalography using the big brown bat (*Eptesicus fuscus*). They found that as in other animals, the hippocampus shows typical high voltage slow activity while maintaining a steady body temperature, but a dramatic change occurs in the hippocampus when the body temperature is falling. The hippocampus showed continu-

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ous 3 per second spike and wave formation which corresponds to the typical EEG pattern seen in human epileptics. This EEG activity occurred whenever the body temperature was falling. Conover (1969) has emphasized the hippocampal role for the lowering of the body temperature of the bat and for entry into hibernation. He has reported that bilateral hippocampal lesions caused very slow entry into hibernation.

It is well known that of all the brain areas, the hippocampus is the most susceptible to epileptic discharge. Koski (1973) has postulated that in the bat, the excitement from cold exposure eventually causes a seizure in the hippocampus, and the seizure is then projected along the fornix (the largest output fibers of the hippocampus) to the posterior hypothalamus. Much experimental work has shown that when a part of the brain is in seizure, it does not perform its normal function. More specifically the seizure turns off the heat conserving mechanisms. Because of this the body temperature falls and the bat enters hibernation.

Based on the hypothesis that hibernation is an epileptic fit, which has been suggested by Koski and his associates, the following would be likely in terms of correlations between body temperature of the bat and certain drugs acting on the central nervous system (CNS) or an epileptogenic intermittent light stimulation (ILS). First, if hibernation is a seizure, diphenylhydantoin (DPH) which is an anticonvulsant should prevent entry into hibernation. In other words DPH should keep the body temperature at a high level when the bat is exposed to cold ambient temperatures. Second, if hibernation is a seizure, the epileptogenic or CNS stimulants such as photic stimulation and pentylenetetrazol (Metrazol) should cause

a fall of body temperature and facilitate entry into hibernation.

The present study has, therefore, been designed in order to test those possibilities in the bat during cold exposure.

MATERIALS AND METHODS

1) Preparation of Animals:

Three kinds of bats were used in the present study: Oriental discoloured bats (*Vesperugo superans*), little brown bats (*Myotis sodalis*), and big brown bats (*Eptesicus fuscus*). The Oriental discoloured bats (22 female bats, weighing an average 13 gm) were captured from roosts on the roof of an old tile-roofed house in Euijeongbu in July and August, 1974. The little brown bats (23 male bats weighing an average 7 gm) and the big brown bats (2 male bats weighing an average 10 gm) were captured from Ray's Cave in the vicinity of Indianapolis in October, 1973.

In the laboratory the bats were housed in a wire-mesh cage and fed mealworms or artificial diet recommended by Uchida (1974). The cage was kept in a cold room or a refrigerator when not in use. The animals were kept in an incubator which was maintained at $36^{\circ} \pm 0.5^{\circ}\text{C}$ when in use, and the humidity was kept at a high level. The bats were given free access to water.

2) Techniques of Data Recording:

When needed for an experiment, a bat was removed from the cage and immediate surgery was performed to implant a small thermocouple beneath the subcutaneous space of the back in the middle of the interscapular region either under light ether anesthesia or without anesthesia. Two pin electrodes for recording

heart rate were inserted into the skin of the right forearm and the left leg respectively. The thermocouple was attached to a Grass polygraph (Model 7, 4 channels) or a telethermometer was used to an accuracy of one tenth of a degrees centigrade ($^{\circ}\text{C}$). The heart rate electrodes were attached to a polygraph and the EKG panel was set to record on aVr. The cold room or refrigerator for the cold exposure was maintained at $4^{\circ} \pm 2^{\circ}\text{C}$ during the experiments. Three parameters, body temperature (Tb), ambient temperature (Ta), and heart rate (HR, beats/minute) were recorded every five minutes during the experiments, and their fluctuations per unit time (hours) were graphed on 5mm mesh graph papers.

3) Administration of Drugs:

To test the effects of diphenylhydantoin (DPH) on body temperature of the bat when exposed to cold, two kinds of bats were used respectively. DPH (60mg/kg, Parke Davis Co.) was intraperitoneally given to the bats 30 to 40 minutes before placing them in the cold room. As a control some animals were treated in the same way with physiological saline solution (PS) or DPH solvent. To test the effects of pentylenetetrazol (Metrazol) on body temperature of the bat under cold conditions Metrazol (10 to 40mg/kg, Parke Davis Co.) was intraperitoneally injected several times during the experiments.

4) Intermittent Light Stimulation (ILS):

To test the effects of light or photic stimulation on body temperature under cold conditions a photostimulator (Intensity 8, 10 to 30 flashes/second, Grass PS 22) was used in the present study. The flickering rate given above is generally regarded as the best rate to cause petit mal seizures in human epileptics

(Walter *et al.*, 1946; Gastaut, 1950).

RESULTS

I. Effects of Diphenylhydantoin (DPH) on Body Temperature of Bats During Exposure to Cold

1. Experiments on the Oriental Discoloured Bats (*Vespertilio superans*)

a) Normal Entry into Hibernation:

Figures 1 to 7 show the changes of body temperature during normal entry into hibernation in the oriental discoloured bats. In Fig. 1 the initial response of the normal bat when removed from the incubator and placed in the cold room was drastic. The Tb fell immediately and reached the level of hibernation within two hours. The Ta was maintained within a 10°C range. In Fig. 2 the changes of Tb was different from that of Fig. 1. The Tb remained high although it fell several degrees after forty minutes. There was a typical plateau which is characterized by a temporary delay in fall of body temperature. The time to reach the hibernation level was similar to that of Fig. 1. In Fig. 3, the change of Tb was similar to that of Fig. 1 although the middle part of the experiment was not recorded because of instrumental difficulties. In Fig. 4 more rapid entry into hibernation was observed and the Tb was fixed at a stabilized level within one hour and fifteen minutes. The Ta was kept at 4°C and hardly varied through the experiment. The heart rate fell drastically and reached a stabilized level (10 beats/minute) within almost the same time as the Tb. In Fig. 5 the Tb decreased in the same way with a brief plateau at twenty minutes, and the bat entered hibernation within two hours. The HR also paralleled the Tb and stabilized at one and half hour point at a

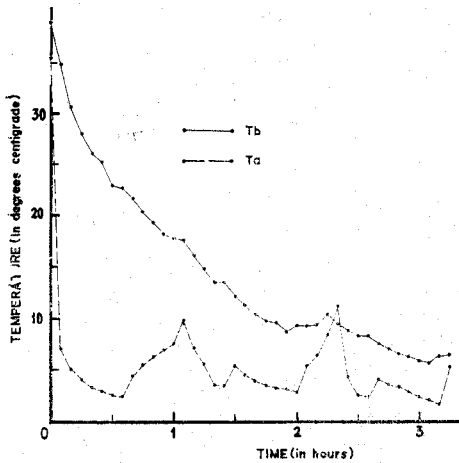


Fig. 1. Normal Entry into Hibernation, Exp-VI, *Vespertilio superans* (13.0 gm).

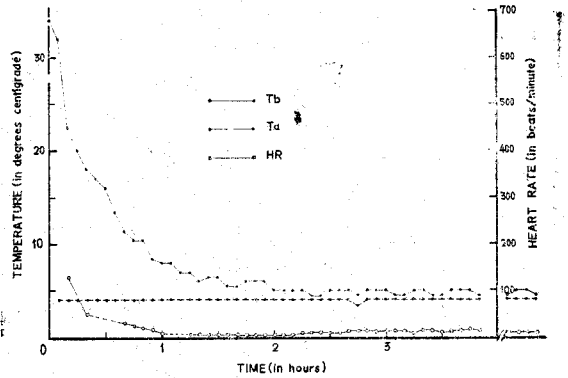


Fig. 4. Normal Entry into Hibernation, Exp.-28, *Vespertilio superans* (12.7 gm).

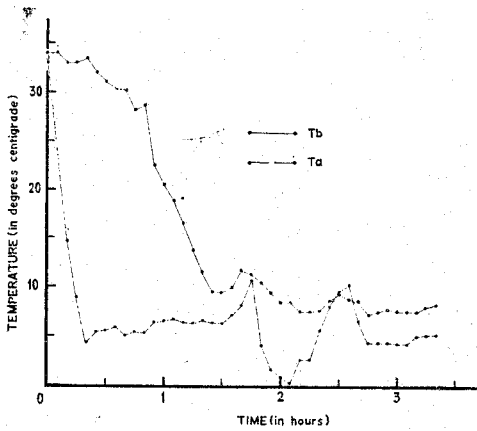


Fig. 2. Normal Entry into Hibernation, Exp.-12, *Vespertilio superans* (14.1 gm).

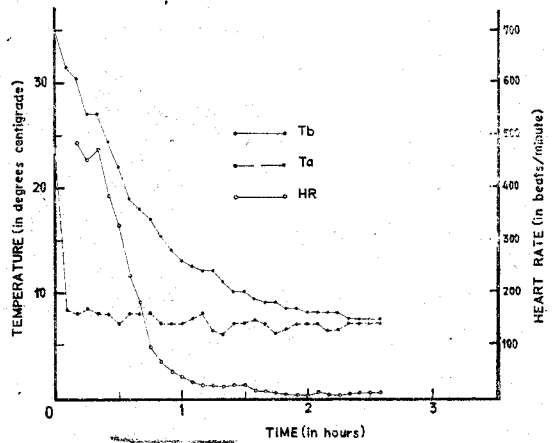


Fig. 5. Normal Entry into Hibernation, Exp.-29, *Vespertilio superans* (14.0 gm).

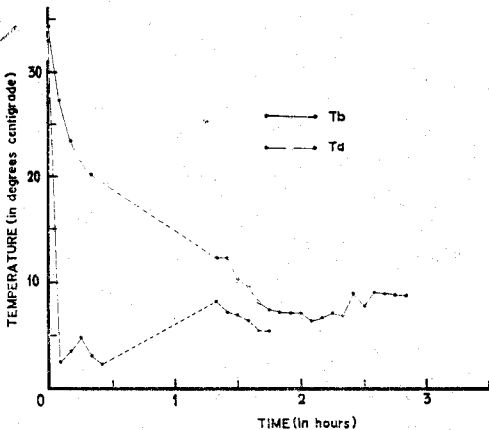


Fig. 3. Normal Entry into Hibernation, Exp.-14, *Vespertilio superans* (13.6 gm).

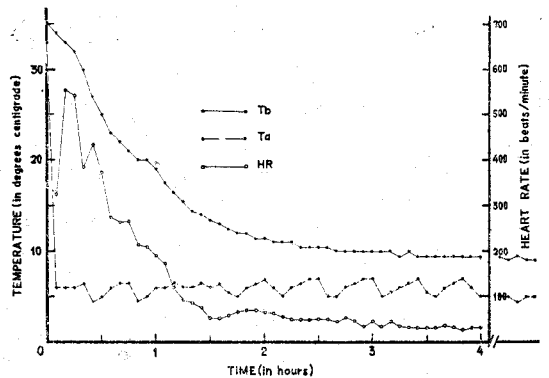


Fig. 6. Normal Entry into Hibernation, Exp.-30, *Vespertilio superans* (14.5 gm).

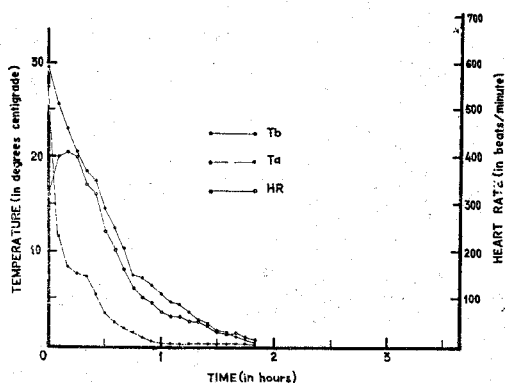


Fig. 7. Normal Entry into Hibernation. Exp.-XXXIV, *Vespertilio superans* (7.7 gm).

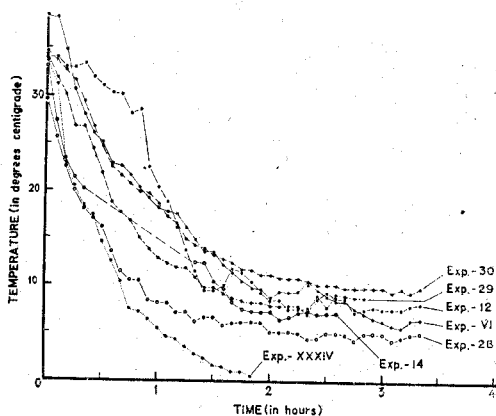


Fig. 8. Normal Entry into Hibernation, *Vespertilio superans* (7 individuals).

rate of 10 beats/minute. In Fig. 6 the drop in Tb was evident from the beginning of the experiment. A typical brief plateau was observed just before the one hour point. An initial dramatic increase of the HR was also observed in the experiment followed by stabilization at 30 beats/minute until the four hour point. Even the following day two parameters (lower and right side of the figure) remained at the same level as the previous day. In Fig. 7 both the Tb and HR curves were similar to those in Fig. 6, but fell earlier. This might be due to the sudden drop of the Ta to the 1°C level.

When the above seven figures are combined with special regard to the changes of Tb only, Fig. 8 may be obtained. The initial responses of Tb were generally drastic and the bats entered hibernation within about two hours. There were no thermoregulation periods which are characterized by up-and-down fluctuations of Tb, although some entries into hibernation were interrupted by brief plateaus. The descending curves seem to be "exponential" in that there is an early rapid drop followed by a gradual leveling, and the Tbs eventually stabilized at a definite level of hibernation.

b) Effects of Physiological Saline Solution (PS) on Body Temperature During Exposure to Cold

Four figures from Fig. 9 to Fig. 12 illustrate the changes of Tb in bats treated with physiological saline solution. In Fig. 9 the initial changes of the Tb was not different from those of normal bats. A relatively longer plateau was found at thirty minutes point, which lasted for 20 minutes. The Tb then decreased and remained at hibernation level. However the HR differed greatly from the Tb, and the drop was drastic. In Fig. 10 the change of the Tb was similar to those in normal bats but the HR was curious, especially in the early response. Right after placing the animal in the cold the initial response was more drastic than that observed in previous experiments. In Fig. 11 the changes of both the Tb and HR were generally identical with those of the normal and the controls except in the last part of the experiment. The Tb fell steadily to 1°C level with only a brief plateau within one and a half hour. This unusually rapid drop of the Tb was thought to be probably due to excessively low Ta (0°C). In Fig. 12 the change of the Tb was characterized by

long and prominent plateaus at 30 minutes and one hour and fifteen minutes respectively.

Combining the above four figures with regard to the changes of Tb only, Fig. 13 may be obtained. The changes of the Tb following the intraperitoneal injections of PS were similar to those of normal bats except that the time intervals were longer.

c) Effects of Diphenylhydantoin (DPH) on Body Temperature During Exposure to Cold

Nine figures from Fig. 14 to Fig. 22 illustrate the effects DPH on body temperature and heart rate of bats during cold exposure. In Fig. 14 the initial change of Tb was drastic but after one hour it differed from those of the normal and PS injected controls. The drop in Tb was slow until the Tb reached 12°C with two distinct plateaus. At three and a

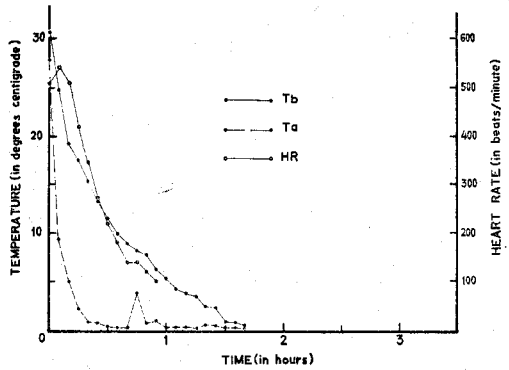


Fig. 11. P.S. inj. Control, Exp-36, *Vespertilio superans* (10.7 gm).

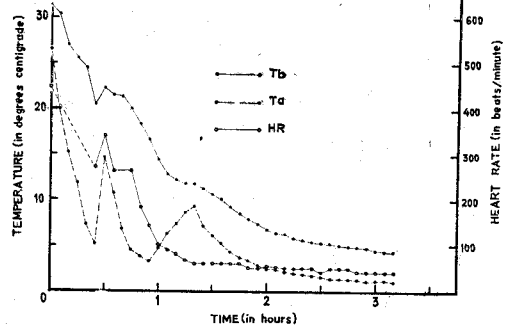


Fig. 12. P.S. inj. Control, Exp-XXIII, *Vespertilio superans* (7.8 gm).

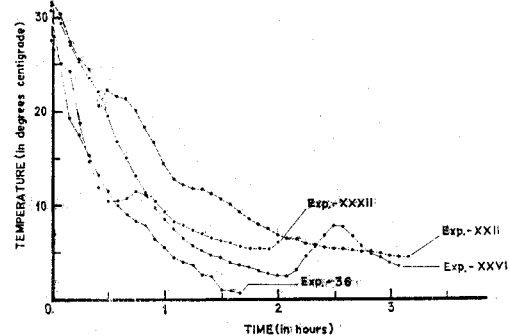


Fig. 13. P.S. inj. Control, *Vespertilio superans* (4 individuals).

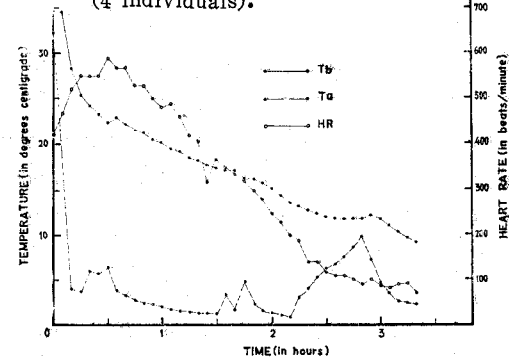


Fig. 14. DPH Effect on Tb and HR, Exp-I, *Vespertilio superans* (14.9 gm).

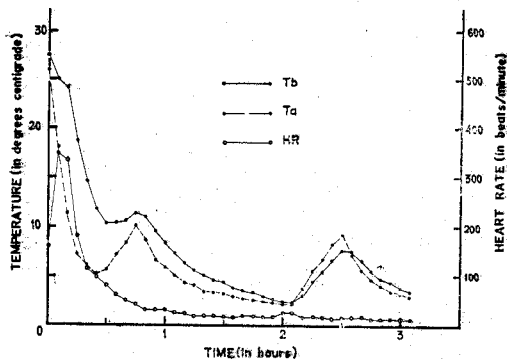


Fig. 9. P.S. inj. Control, Exp-XXVI, *Vespertilio superans* (7.1 gm).

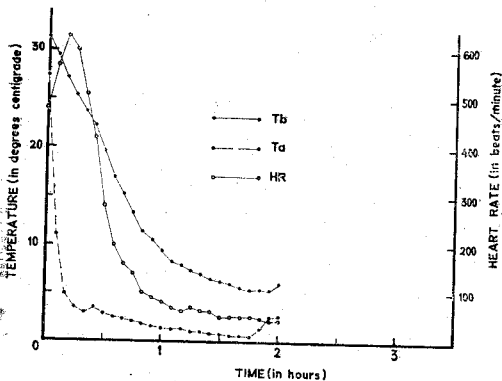


Fig. 10. P.S. inj. Control, Exp-XXXII, *Vespertilio superans* (11.4 gm).

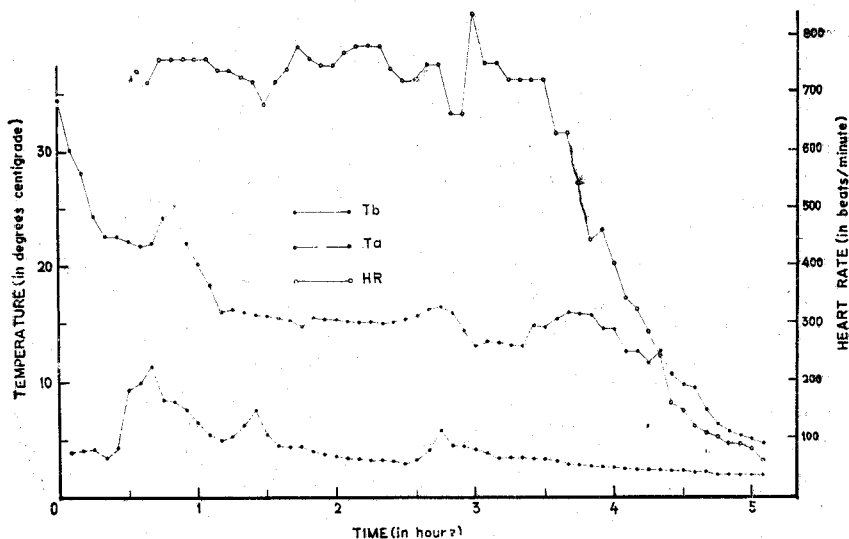


Fig. 15. DPH Effect on Tb and HR, Exp-III, *Vespertilio superans* (14.7 gm).

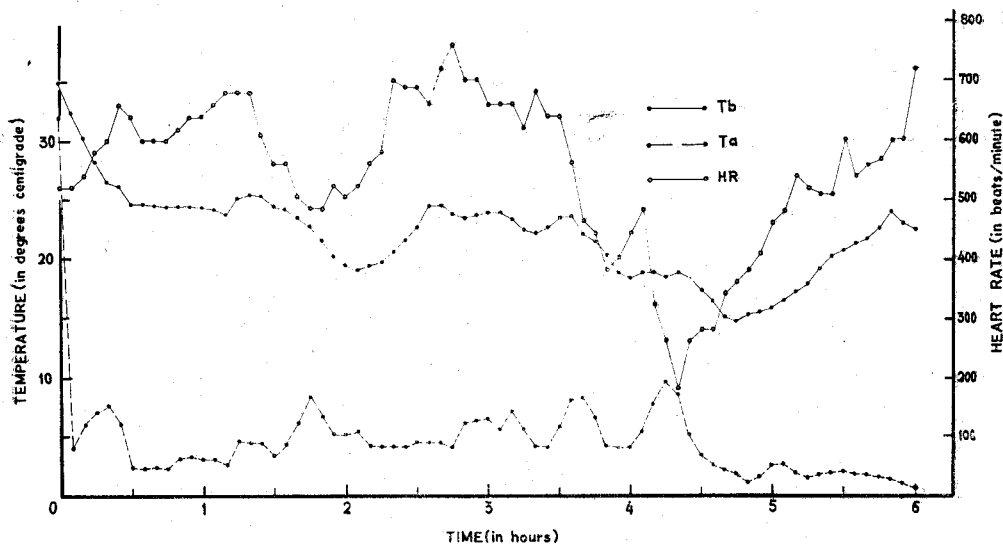


Fig. 23. DPH Effect on Tb and HR
Vespertilio superans (9)

Fig. 16. DPH Effect on Tb and HR, Exp-IV, *Vespertilio superans* (15.0 gm).

half hours the bat entered hibernation. The HR was quite different from those of the normal and the PS injected controls. It remained

high at 400 beats/minute or more until one and half hours after which there was a steady decline to the hibernation level. In Fig. 15 a

long and prominent plateau was followed after the drastic initial response until almost four hours, and then the bat entered hibernation. It was surprising to note that this high and long maintenance of Tb has never been found in the normal or the PS injected controls. Moreover, the HR was curious compared with those of the previous experiments. An extremely high and continuous level (750 beats/minute) was observed for three and a half hours followed by a steady fall with two brief interruptions to the hibernation level (50 beats/minute). In Fig. 16 after an initial rapid drop of Tb the curve seemed to be "set" at the level of 20°C as early as 30 minutes. In this experiment the bat never entered hibernation until after six hours. In Fig. 17, 19, 20, 21 and 22 the changes of Tb following DPH administration were almost similar to those shown in the normal and PS injected controls except for several longer plateaus. In Fig. 18 the initial response and the change thereafter were similar to those of the other DPH experiments until one and a half hours, and then the bat entered hibernation within three and a half hours. The HR curve was characterized by two large up-and-down fluctuations during the high maintenance of Tb.

In Fig. 23 the above nine figures have been combined with special regard to the changes of Tb. In Fig. 23 one can recognize that the early responses of Tb to the cold in the bats treated with DPH were similar to those of the normal and the PS injected controls, but later changes of Tb were remarkably varied. The striking effects of DPH on body temperature and heart rate of the bats were evident in seven of nine experiments. In the remaining two experiments (Fig. 17 and 19), no distinct differences were found compared with the normal and PS injected controls.

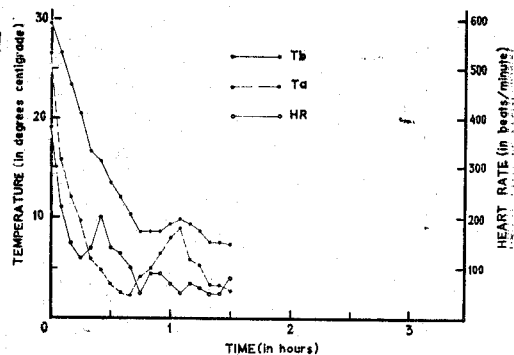


Fig. 17. DPH Effect on Tb and HR, Exp-XVII, *Vespertilio superans* (7.6 gm).

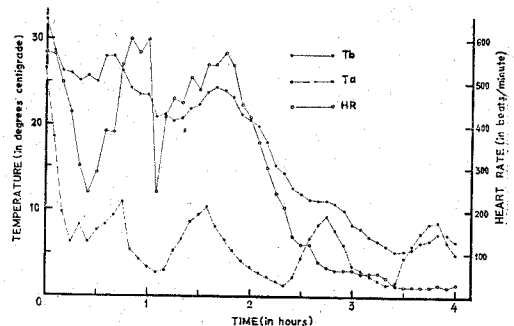


Fig. 18. DPH Effect on Tb and HR, Exp-XIX, *Vespertilio superans* (8.0 gm).

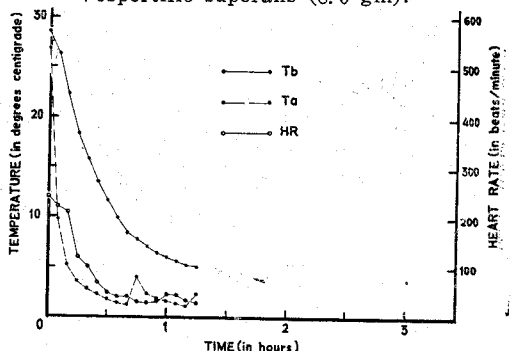


Fig. 19. DPH Effect on Tb and HR, Exp-XXI, *Vespertilio superans* (7.5 gm).

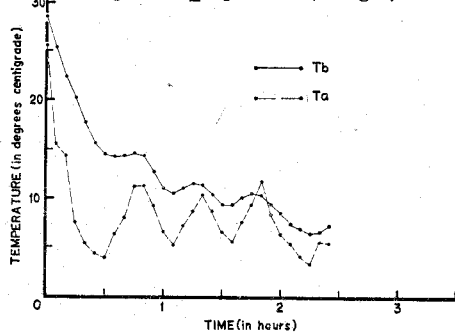


Fig. 20. DPH Effect on Tb Exp-20, *Vespertilio superans* (15.5 gm).

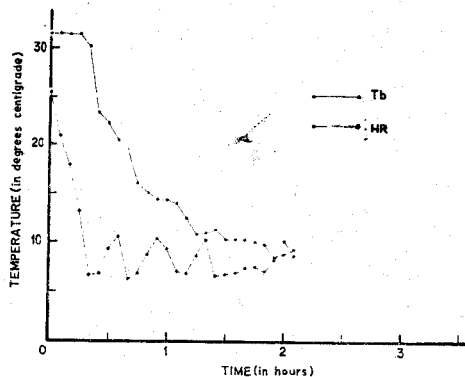


Fig. 21. DPH Effect on Tb, Exp-18, *Vespertilio superans* (15.5 gm).

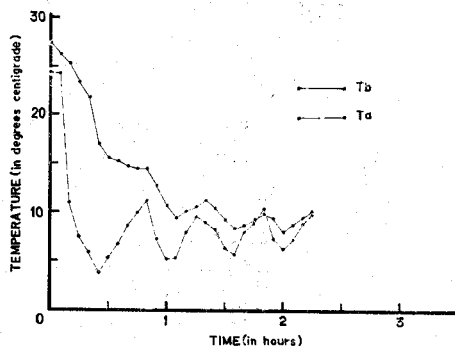


Fig. 22. DPH Effect on Tb, Exp-16, *Vespertilio superans* (15.0 gm).

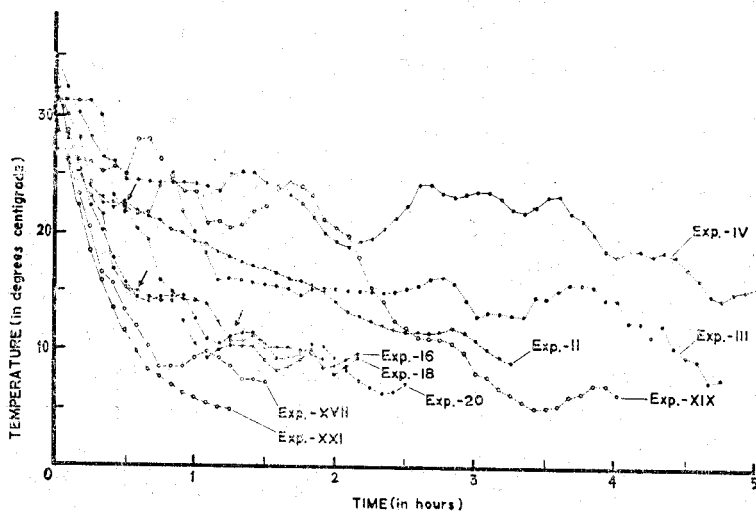


Fig. 23. DPH Effect on Tb and HR, *Vespertilio superans* (9 individuals).

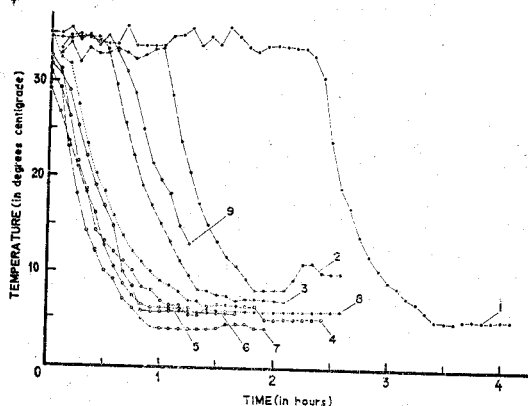


Fig. 24. Normal Entry into Hibernation, *Myotis sodalis* (9 individuals).

2) Experiments on the Little Brown Bats (*Myotis sodalis*)

a) Normal Entry into hibernation

Fig. 24 illustrates the changes of body temperature when nine little brown bats are placed in the cold room. In Fig. 24 eight of nine bats showed similar responses as far as the entry into hibernation was concerned, although three of them (2, 3 and 9) were delayed for thirty to fortyfive minutes. The initial drastic falls of Tb were also recognized in

five(4, 5, 6, 7 and 8) experiments. All the bats except for No. 1 entered hibernation within two hours without any plateaus. The No.1 experiment was unusual in that a typical long thermoregulation period lasted for two and quarter hours, but no plateau was found on the descending course of Tb.

b) Effects of diphenylhydantoin (DPH)-Solvent on Body Temperature During Exposure to Cold

Fig. 25 shows the effects of diphenylhydantoin(DPH)-solvent on Tb of the bat during cold exposure. In Fig. 25 the changes of Tb in the first three (1, 2 and 3) bats were similar to those of the normal bats. They entered hibernation within one and a half hours and the Tb stabilized at 7°C level. But the No. 4 bat showed an unusual delayed pattern of entry into hibernation. The Change of Tb in the No. 5 bat was extremely curious in that the initial drastic drop of Tb was not found, and the thermoregulatory period characterized by up-and-downs lasted for four hours or more, although sudden drops of large scale were temporarily evident at one half and three hours respectively. In all the bats except for one, the entry into hibernation was rapid once it began.

c) Effects of Diphenylhydantoin(DPH) on Body Temperature During Exposure to Cold

Fig. 26 illustrates the effects of diphenylhydantoin(DPH) on body temperature of the little brown bats. In experiments No. 1, 2 and 3 a remarkable thermoregulation period was observed, which was maintained until two to two and a half hours. The Tb stabilized at roughly 9°C at four hours. It is notable that there were also long plateaus in experiments 4, 5 and 6, that were absent from the normal and DPH-solvent controls. The change of Tb

in the experiment was similar to that of the normal and controls, especially in the later part of the experiment. However, there was no initial drastic fall of Tb although a brief but distinct plateau was evident at one half hour. None of the curves showed any drastic initial drop in these experiments, in contrast to those frequently found in the normal and the DPH-solvent controls.

II) The Effects of Intermittent Light Stimulation(ILS) on Body Temperature of Bats During Exposure to Cold

Fig. 27 shows the effects of intermittent light stimulation (ILS) on body temperature of the big brown bat during the entrance phase of hibernation. In Fig. 27 the Tb remained high for one and a half hours and at this point, the first ILS was applied. The Tb dropped immediately to 23°C, followed by a rise to the thermoregulation level. The second ILS was then turned on, but this time for only 10 seconds. This short ILS caused a drop in Tb. It is interesting to note that this second drop was almost identical to the first drop, even though the ILS was so brief. The third ILS was made to bring the hibernation level by long and continuous stimulation. The Tb was stabilized in 7°C at the eight hour point.

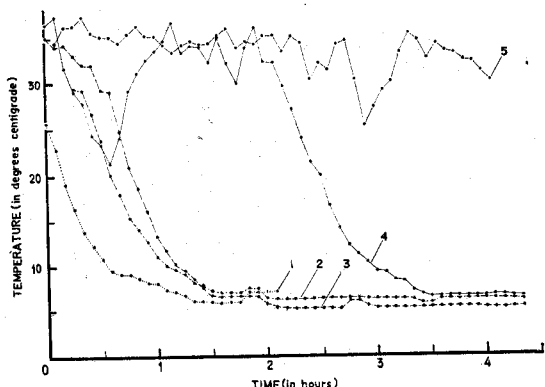


Fig. 25. DPH Solvent Control, *Myotis sodalis* (5 individuals).

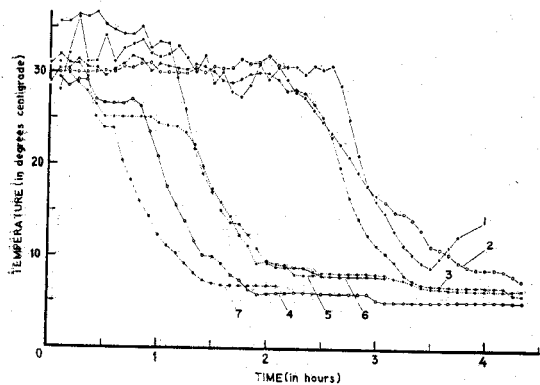


Fig. 26. DPH Effect on Tb, *yoti sodalis* (7 individuals).

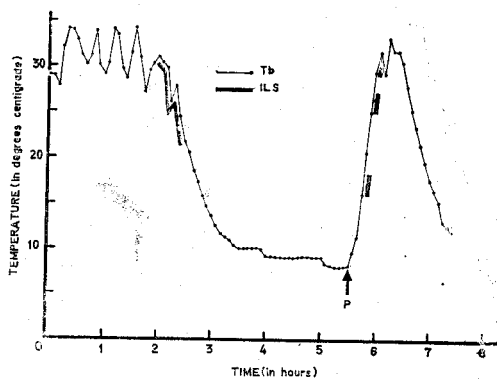


Fig. 29. ILS Effect on Tb, Exp-(IIa), *Eptesicus fuscus* (17.8 gm).

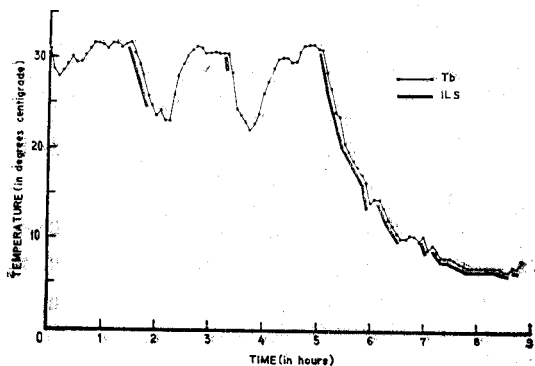


Fig. 27. ILS Effect on Tb, Exp-(Ia), *Eptesicus fuscus* (20.0 gm).

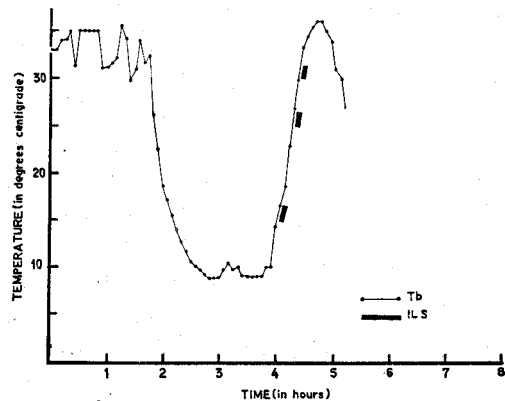


Fig. 30. ILS Effect on Tb, Exp-(IIb), *Eptesicus fuscus* (17.8 gm).

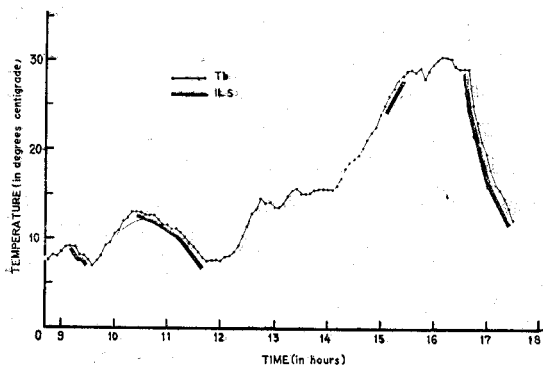


Fig. 28. ILS Effect on Tb, Exp-(Ib), *Eptesicus fuscus* (20.0 gm).

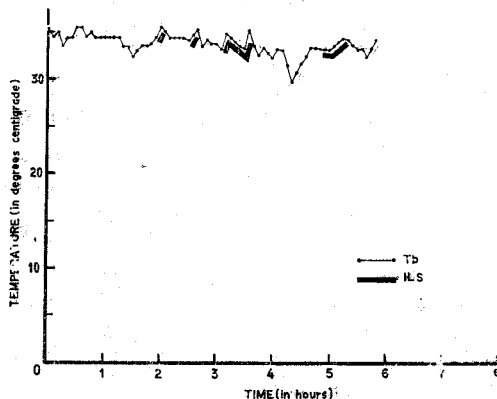


Fig. 31. ILS Effect on Tb, Exp-(IIc), *Eptesicus fuscus* (22.9 gm).

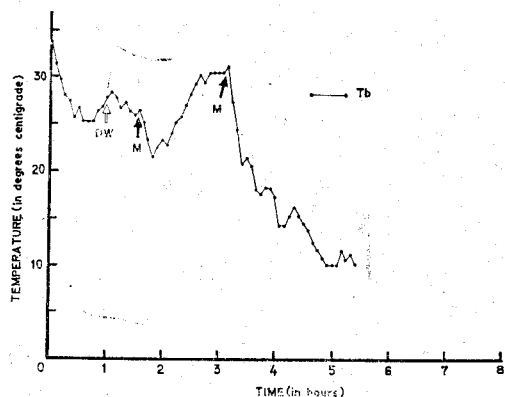


Fig. 32. Metrazol Effect on Tb, Exp-(IIIa), *Myotis sodalis* (8.38 gm).

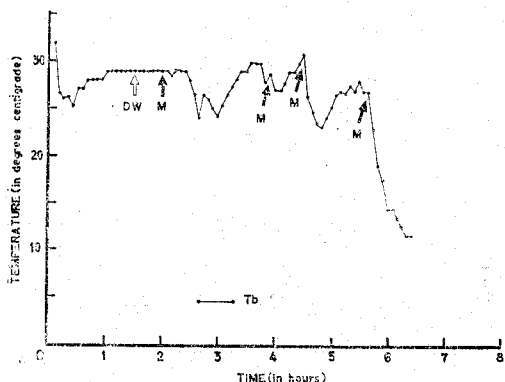


Fig. 33. Metrazol Effect on Tb, Exp-(IIIb), *Myotis sodalis* (7.5 gm).

Fig. 28 shows a continuation of the same experiment (Fig. 27). When the ILS was turned off for twenty minutes the Tb rose to 9°C. Then the ILS was turned on again, and then the Tb fell. The ILS was again turned on at the 13°C point and the Tb again fell to the hibernation level. Then for a long period the ILS was kept off. The bat raised its Tb as in arousal from hibernation. When the Tb had reached 25°C the ILS was turned on for twenty minutes. It was surprising to notice that the ILS this time had no effect; the Tb did not fall. After the arousal was finished at

sixteen hours, the long ILS was turned on again. The bat was again sensitive to the flicker, and the Tb fell.

Fig. 29 shows results of another experiment with the big brown bat to test the effects of ILS on body temperature. During thermoregulation the Tb remained high for two hours. At the end of two hours the ILS was turned on for thirty minutes. This flicker stimulation caused the Tb to fall to the 10°C level, and the bat eventually entered hibernation. After two hours of hibernation, the bat was pinched for five minutes as indicated by an arrow (P). The pinching caused the bat to be aroused from hibernation as expected. During the arousal, three brief ILSs were applied when the Tb was at 15°, 25° and 30°C respectively. The ILS, as in the Fig. 28, had no effect on the Tb. After the arousal this bat reentered hibernation by itself.

Fig. 30 illustrates more evidence to demonstrate that during the arousal the ILS cannot cause the Tb to fall. The same applications as in the former experiment were made but without effect.

Fig. 31 shows the results of another experiment performed using the same bat used in the former experiments (Fig. 29 and 30). Six days after the last experiment, the same bat was used again to test sensitivity to the flicker. During the long thermoregulation period, several applications of ILS (two times for 5 minutes and two times for 30 minutes) were made but without effect. After five hours, the thermoregulation still remained active. The bat was no longer sensitive to the ILS.

III) The Effects of Pentylenetetrazol (Metrazol) on Body Temperature of Bats During Exposure to Cold

Fig. 32 and Fig. 33 show the effects of pe-

metrazol(Metrazol) on body temperature in the little brown bat. In Fig. 32 at the white arrow an intraperitoneal injection of distilled water(DW) was administered. There was no effect. One half hour after the first injection of 40 mg/kg of Meterazol as indicated by the first black arrow (M), a sudden drop in Tb was observed followed by recovery to the thermoregulation level. After the second injection (40 mg/kg) of metrazol, the change of Tb was remarkable and fell to the hibernation level with brief but prominent plateaus.

Fig. 33 illustrates results of another experiment to test the Metrazol effect on Tb in the same bat (Fig. 32). For one and a half hours this bat thermoregulated in the cold. At the white arrow DW was administered but there was no effect. Then at the first black arrow, 10mg/kg of Metrazol was injected and a small drop in Tb was observed. Both the second (20 mg/kg) and third (30 mg/kg) injection of Metrazol caused large drops, but Tb recovered again to the thermoregulation level. The last (40 mg/kg) injection was applied at five and a half hours. This time Tb fell drastically to 10°C and the bat entered hibernation. This bat could not be awakened by pinching.

DISCUSSION

Since Putnam and Merritt (1937) established the effectiveness of diphenylhydantoin (DPH) by administering it to cats in which convulsions were electrically induced, much supporting evidence has been reported. As a result DPH was quickly labelled an antiepileptic and anticonvulsant. However, we now know that the discovery was even more remarkable than originally thought. It has long been known that DPH stabilizes nerve cells against hyper-

excitability, not only in vertebrates but also in invertebrates. Morrell *et al.* (1959) have shown that DPH is superior to phenobarbital in blocking cortical spread of seizure activity from an induced focus. On the other hand, Nakamura and Kurube(1962) have reported that DPH elevated the hippocampal seizure threshold and suppressed propagation with no effect on the after-discharge pattern. Schallek and Kuehn(1963) have also found in studies of deep electrode stimulation in cats that the duration of cortical and hippocampal response decreased when using DPH. Riehl and McIntyre (1968) have demonstrated that electroencephalogram discharges from abnormal sites were decreased by DPH while no changes occurred in those of normal controls.

According to the results of the above authors and other workers, it seems clear that the hippocampus is closely related to certain-seizure activity occurring in the brain, and DPH is, to some extent, able to modify and depress its propagation and/or hippocampal threshold. Conover(1969) has reported on the effects of bilateral hippocampal lesions in the bat. He states that most lesioned bats showed a very slow entry into hibernation. In other words, when the hippocampus is not able to work properly the ability to lower body temperature is severely impaired, which means that the hippocampus is closely related to the heat producing mechanism of the body. It therefore seems likely that the remarkable effects of DPH observed in the present study are closely related to the antiepileptic function of the hippocampus.

Whatever the mechanism by which the drop of Tb during cold exposure took place in the present experiments, the effects of DPH on body temperature of bats were clear, providing further support for the seizure theory of hi-

bernation proposed by Koski and his coworkers. At the same time, the present results provide more evidence in support of the anti-convulsant effects of DPH as demonstrated in the baboon by Stark *et al.* (1970). First, the onset of entry into hibernation seemed delayed in DPH-treated bats in both the oriental discoloured bats and the little brown bats. Second, the entry into hibernation in DPH-treated bats was evidently interrupted by long plateaus during which the fall of Tb temporarily ceased. This cessation of temperature drop is thought to be represented by seizure activity that lowers the body temperature. In other words, since the hypothalamus is not in a state of seizure, probably due to an elevation of threshold caused by DPH, it produces heat to cause the plateau of the curve. Finally, the delayed entry into hibernation displayed by a large number of the DPH-treated bats is explained by the idea that the normal rapid seizure, proceeding the bats entry into hibernation, is less strong and can not lower the Tb at the normal rate.

It is well known that the most distinctive EEG pattern within the idiopathic or non-focal group is the bilateral charge of 2.5 to 3.5 cycles per second(cps) spike and that the discharge can usually be precipitated by hyperventilation and often by photic or light stimulation (Marcus, 1972). Killam *et al.* (1966a) have discovered that the baboon, *Papio papio*, has brief seizures when visually exposed to flickering. This discovery is important since it presented the first natural animal model of a human epileptic seizure. It is interesting that only the baboons from Senegal in Africa showed ILS epilepsy while those from outside Senegal were not sensitive to the light stimulation. As far as the present hypothesis is concerned, however, it is important to note the

fact that light stimulation can precipitate an idiopathic (petit mal) epilepsy that is characterized by a specific 3 spike and wave pattern. Gerhardt and Koski(1973) have demonstrated in studies of bats implanted with EEG electrodes that the hippocampus shows continuous 3 per second spike and wave EEG formation when the body temperature falls, a pattern which continues as long as the Tb is in decline. This response is exactly like that observed in human epileptics during petit mal seizure.

It was surprising to note in the present study that whenever the ILS was applied, either briefly or for long periods, the bat's Tb fell dramatically, even to the hibernation level if given steadily. This is strong evidence that the ILS has induced true hibernation since all the bats could raise their Tb in the cold when they were pinched, as indicated by an arrow(P) in figure 29. It was interesting that none of the bats was sensitive to the ILS while they were awakening from hibernation, as shown in Fig. 28, 29 and 30. These figures illustrate the fact that when the heat producing mechanism once begins to work properly it persists to the end until the Tb rises to the active or thermoregulatory level(30°C or more). It is also interesting that the bat is not always equally sensitive to the flickering light stimulus from one day to the next, as in the experiments on the baboon by Killam *et al.* (1967a, 1967b). In the present study the same bat was reexamined six days after the last experiment, at which time there was no longer evidence of sensitivity to the ILS. Further study should be designed to confirm the effects of ILS on Tb during exposure to cold in order to obtain firm evidence.

Esplin(1972) has emphasized that pentylene-tetrazol (Metrazol) has clearly been of the

most value as a laboratory tool in inducing chemical seizures that resemble some forms of petit mal epilepsy, even though studies with a variety of neuronal models have failed to give definitive clues to the basic action of Metrazol. Bruns *et al.* (1950) have demonstrated in studies on rabbits that subcutaneous injection of Metrazol resulted in a fall of Tb. Shemano and Nickerson (1959) have reported that ambient temperature plays a major role in determining thermal responses to many drugs and that there is a critical Ta above which a given drug produces a rise in Tb and below which a hypothermic response is evoked. They have observed in studies on dogs that convulsive doses (15mg/kg each at 20 minutes, seven times) produced a consistent hyperthermia at Ta above 23° to 25°C, and a consistent hypothermia at lower temperatures. They have also indicated in experiments on dogs, with the spinal cord acutely sectioned at the C₄ to C₆ level, that the thermal responses to Metrazol are of central origin, but are not simply the result of an induced poikilothermia. According to Hahn *et al.* (1963) such a thermal response to Metrazol seems to vary in accordance with animal conditions, including normal status or anesthesia. The hyperthermia, therefore, was considered by them to be an expression of a temporary lability of the heat regulating system during artificial arousal of the animals.

In the present study it was apparent that intraperitoneal injection of Metrazol caused considerable decrease in the body temperature of the little brown bat. This was further support for Shemano and Nickerson's view in that a hypothermic response was evoked below a critical Ta, even though the experimental animals were quite different from those in the present study. With smaller doses of

Metrazol, around 30mg/kg, the fall of Tb was reversible and the bat could rewarm its body to the active level. Larger doses of Metrazol, 40 mg/kg or more, caused a drop in Tb which can not eventually be reversed. The Metrazol experiments indicate that convulsive doses can cause a fall in the Tb of the bat, and that these results may be further support for the epileptic theory of hibernation proposed by Dr. Koski and his coworkers.

Finally, the author would like to ask the question which has been the main title of research works promoted by many researchers (Koski, 1968; Gerhardt and Koski, 1973; Conover, 1969; Meyers, 1976; Oh and Koski, 1974) Is hibernation an epilepticfit? The author thinks that, based on the above experiments, the answer should be yes. It may seem peculiar at first that such a beneficial process as hibernation should be based on what we think of as a disease. However, it is a fortunate circumstance that prominent experimental results affirming the hypothesis have been reported recently.

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