EFFECTS OF HYPOTHALAMIC LESIONS ON THYROID ACTIVITY OF HIBERNATING GROUND SQUIRRELS (*CITELLUS TERETICAUDUS*)

by

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ABSTRACT

Hibernating ground squirrels, Citellus tereticaudus, were placed in an environmental chamber at low ambient temperatures (5°C) after electrolytic lesions were produced in various areas of the hypothalamus. Lesions located in the anterior hypothalamus were correlated with a significant decrease in I^{131} uptake by the thyroid gland. Changes in the cytological structure of these thyroid glands were also indicative of a decrease in activity. The thyroid glands of control ground squirrels, and squirrels with sham lesions were normal as measured by I^{131} uptake and cytological examination. At an ambient temperature of 5°C ground squirrels with anterior hypothalamic lesions dropped their body temperature to 6°C to 8°C and died shortly thereafter, while control squirrels, and squirrels without such lesions either maintained their body temperature around 29°C or exhibited fluctuation from 32°C to 6°C. It appears that anterior hypothalamic lesions in Citellus tereticaudus cause a decrease in I^{131} uptake by the thyroid and in body temperature. Squirrels with anterior hypothalamic lesions are unable to fluctuate their body temperature and die after approximately 45 hours in hibernation.

INTRODUCTION

Vidovic and Popovic (1954) have reported that the thyroid glands of active ground squirrels exhibit a reduction in ability to accumulate I^{131} during September and October when hibernators initially enter hibernation. These investigators have also reported that the thyroid gland of hibernating ground squirrels does not concentrate I^{131} from December to February when hibernators are in deep hibernation. Hoffman and Zarrow (1958) have reported that the thyroid gland of Citellus tridecemlineatus exhibits a decrease in follicle cell height in June when hibernators are active, but initially begin preparation for hibernation. Minimal thyroid follicle cell height was observed from August to January. Hoffman and Zarrow (1958) have also reported a reduction in the amount of stored colloid in the thyroid gland of ground squirrels from June to January. Adler (1926) observed that hibernation can be disrupted by the injection of thyroid extracts into hibernating hedghogs and this result led him to postulate that a reduction in thyroid activity was necessary for hibernation. The above observations indicate that a reduction in thyroid activity occurs during preparation for hibernation as well.

Investigations of the golden hamster exposed to cold (Tashima, 1965) have shown a reduction in thyroid follicle cell height which is in contrast to the observed increase in cell height that follows cold exposure of non-hibernators. However, in contrast to many previous findings, I^{131} uptake (Tashima, 1965) was greater in cold exposed hamsters than in non-cold exposed hamsters and indicates that the thyroid glands of the cold exposed hamsters are, in fact, more active than their histology indicates and more active than the glands of hamsters not exposed to cold. Similarly, histological studies of the thyroid gland of the garden dormouse (Kayser, Lachiver, and Rietsch, 1958), have revealed extremely active glands in August when the animals enter hibernation. Recently, Hudson (1968) observed that injection of thyroxine into Citellus tereticaudus during hibernation was ineffective in preventing torpor. Thus, the observations by Tashima (1965), Kayser, Lachiver, and Rietsch (1958), and by Hudson (1968) have indicated that an inactive thyroid gland is not a prerequisite for preparation and initiation of hibernation.

Changes in neurosecretory activity of the hypothalamus alter the rate of secretion of pituitary thyrotrophic hormone (Mittler, Reeding, and Schally, 1969; Averill, 1969) and thus alter the rate of thyroxine secretion from the thyroid gland. Suomalainen and Nyholm (1956) have observed only a slight amount of neurosecretory

material in the hypothalamus of the hedgehog during July and August when this hibernator is active. In September and October, more neurosecretory material was observed as the hedgehog entered hibernation and the axons of the tract were quite thick indicating that the secretory substance was being stored. During deep hibernation from November to March the axons stained well, but they appeared thin indicating that secretion was intense. Likewise, Petrovic and Kayser (1958) have shown that homografting the pituitary gland initiates thyroid activity earlier than usual in the hibernating hamster (Cricetus cricetus). The intense hypothalamic neurosecretory activity shown by the depletion of neurosecretory substance in the hedgehog hypothalamus and the thyrotropic action of the transplanted pituitary in the hamster suggest that the pituitary gland, and hence the thyroid gland, is actively inhibited by the hypothalamus in these hibernating species.

The observations described above imply that disruption of hypothalamic function may also disrupt thyroid function during hibernation. The manner in which thyroid function is altered during hibernation should be indicative of either an inhibitory or a stimulatory hypothalamic control over the thyroid gland. In addition, it may be possible to correlate abnormal responses to reduced ambient temperatures with specific hypothalamic regions. Therefore,

in the present investigation, various areas of the hypothalamus of the ground squirrel, Citellus tereticaudus, were lesioned and the animals were placed in an environmental chamber at low ambient temperatures. In addition, thyroid activity was determined by the uptake of injected I^{131} and by histological study. Aberrations in thyroid function and/or the manner in which hibernators respond to lowered ambient temperatures was then correlated with specifically lesioned areas of the hypothalamus.

MATERIALS AND METHODS

Eighty ground squirrels, Citellus tereticaudus, were trapped between February and July 1968 in the Catalina Mountain region three miles north of Tucson, Arizona. All animals were maintained on a diet of Purina mouse chow supplemented by small pieces of apples and small quantities of sunflower seeds.

Twenty-nine ground squirrels were lesioned for this investigation during August and September, but a post-operative mortality of 35% reduced this number to 19 lesioned animals. Four animals died one or two days after placement in the environmental chamber at approximately 20°C. Fifteen lesioned animals survived the gradual drop in environmental temperature to 5°C. These animals were injected with I^{131} and data were obtained on the activity of their thyroid glands.

All operated animals were anesthetized by an intraperitoneal injection of 50 mg/cc sodium pentobarbital with the formula of 50 mg of anesthesia per 100 g of body weight. Operated animals were picked at random and were not separated on the basis of sex or weight. Approximate stereotaxic coordinates were determined by correlating histological studies of the squirrel brain with X-rays of the

skull. Final placement of the electrode was made on a modified Stellar stereotaxic instrument utilizing the X-ray technique described by Egge and Chiasson (1963). Bilateral electrolytic lesions were made approximately 0.75 mm to either side of the midsaggital suture and approximately 8 mm below the dural surface by direct anodal current. The intensity varied from 2 to 3 ma for 20 to 30 seconds. All animals received a postoperative intramuscular injection of 0.5 ml of penicillin G (300,000 U/ml) immediately after the operation, and the animals were placed in individual cages. Three weeks of recuperation were allotted the animals before they were placed in the environmental chamber.

Throughout the investigation an eight-hour light and 16-hour darkness photoperiod was maintained. The temperature of the environmental chamber was initially set at 20°C, and thereafter, the temperature was dropped in increments of 1, 2, or 3 degrees every other day until a minimum temperature of 5°C was reached. Body temperature was recorded periodically with a quick-change rectal thermometer.

One week after all animals were believed to be hibernating, 0.5 cc of 0.01 mC carrier-free NaI^{131} was injected intraperitoneally into each animal. Uptake of I^{131} by the thyroid gland was measured by placing the neck

region of the animal over a scintillation well-type counter and counting for one minute. Counts were corrected for background and decay and divided by the animal's body weight in grams. Specific activity was then plotted against time in hours.

Immediately after the completion of counting, animals were decapitated and autopsies were performed. The brains and thyroid glands were removed and fixed in Bouin's solution. Both brains and thyroid glands were sectioned at 10 μ, and the brain sections were stained with aldehyde thionin (Paget, 1959) while thyroid sections were stained with haematoxylin and eosin. Lesion locations were verified with the aid of a stereotaxic atlas for the rat brain (König and Klippel, 1963). Lesions were generally asymmetrical and approximately 2.3 mm in diameter. Lesions placed in the anterior hypothalamus were approximately 8 mm anterior to the interaural line. The anterior border of the lesions did not extend beyond the anterior commissure. The posterior border of these lesions never extended more than 0.6 mm caudal to the optic chiasma. Several lesions extended medially into the third ventricle. Six of the eight lesions extended ventrally into the optic chiasma, but never through it.

RESULTS

Thyroid uptake of I^{131} measured at various time intervals is presented for each lesioned and control squirrel in Table 1. The effect of hypothalamic lesioning on thyroid activity is clearly shown in the plot of mean thyroid activity (± 2 standard deviations) in Figures 1 and 2. Control squirrels A through H and lesioned squirrels 9 through 14 exhibited similar thyroid responses to low ambient temperature (5°C) and to hibernation. Control squirrel I and lesioned squirrel 15 exhibited high uptake of I^{131} as compared to the previously mentioned squirrels. Lesioned squirrels 1 through 8 exhibited thyroid activity below that of any other lesioned or control squirrels.

Histological examination of the brains revealed that lesioning had damaged the anterior hypothalamus in squirrels 1 through 8. Lesions were approximately 2.3 mm in diameter, and each damaged more than one group of nuclei, but the anterior hypothalamus was the only commonly damaged area for squirrels 1 through 8 (Figure 3). The brain lesion in squirrel 15 was anterior and medial to the anterior hypothalamus, and it damaged the nucleus preopticus medialis. The lesions in squirrels 9 through 14 were anterior and lateral to the anterior hypothalamus, and they

Table 1. Influence of lesioning, cold exposure, and hibernation on the uptake of I^{131} by the thyroid gland.

Lesioned Squirrels	Hours after injection of I^{131}								
	2	5	12	24	37	44	60	71.5	80
	CPM I^{131} / body wt.								
1	7	7	8	7	9	13			
2	38	39	6	4	8	6			
3	38	42	41	40	42	39			
4	4	6	8	8					
5	10	10	15	16	16				
6	16	8	13	14	15				
7	3	2	4	3	4				
8	12	12	15	17	16				
9	78	116	207	240	224	228			
10	68	101	116	115	106	116	99	73	96
11	74	197	112	105	107	125	110	99	117
12	62	65	75	74	76	85	68	70	74
13	98	129	119	116	106	106	91		
14	112	151	222	177	185	199	176	178	170
15	370	401	437	450	396	370	350	338	338
Controls									
A	59	79	78	86	81	78	70	62	68
B	128	157	179	208	177	178	194	184	147
C	73	105	99	91	87	83	80	75	71
D	82	106	192	191	185	180	190	194	142
E	84	83	70	81	80	76	66	68	65
F	121	138	140	145	116	116	117	115	106
G	132	120	123	121	109	132	100	100	98
H	95	76	77	76	63	60	52	41	41
I	234	247	290	296	292	275	240	229	222

1 through 8 had anterior hypothalamic lesions; 9 through 15 were sham lesioned squirrels.

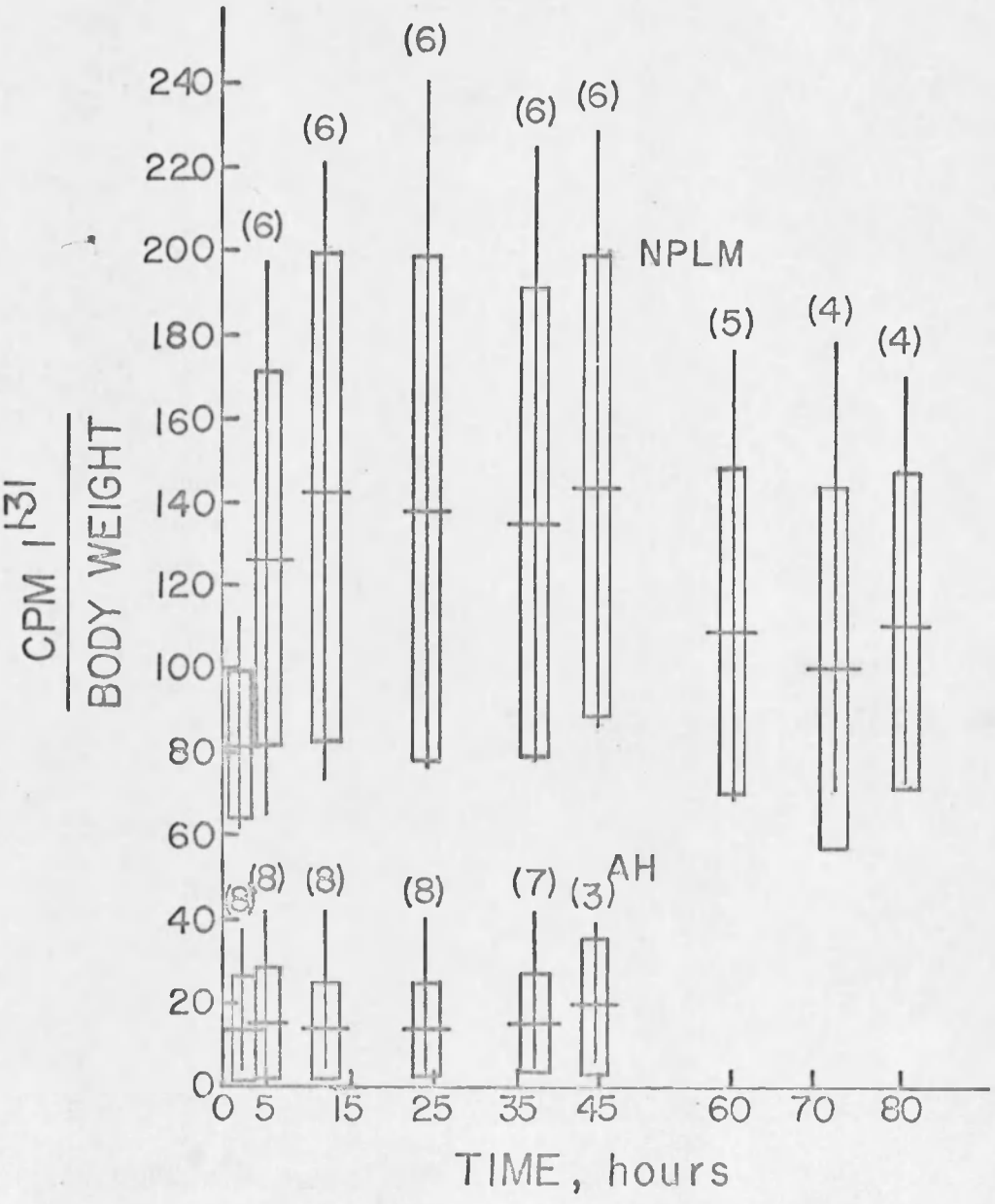

Figure 1. Mean thyroidal I^{131} uptake (± 2 standard deviations) of lesioned ground squirrels.

NPLM = squirrels 9 through 14 with nucleus preopticus lateralis and medialis lesions. AH = squirrels 1 through 8 with anterior hypothalamic lesions. Numbers in parenthesis represent the n number of squirrels.

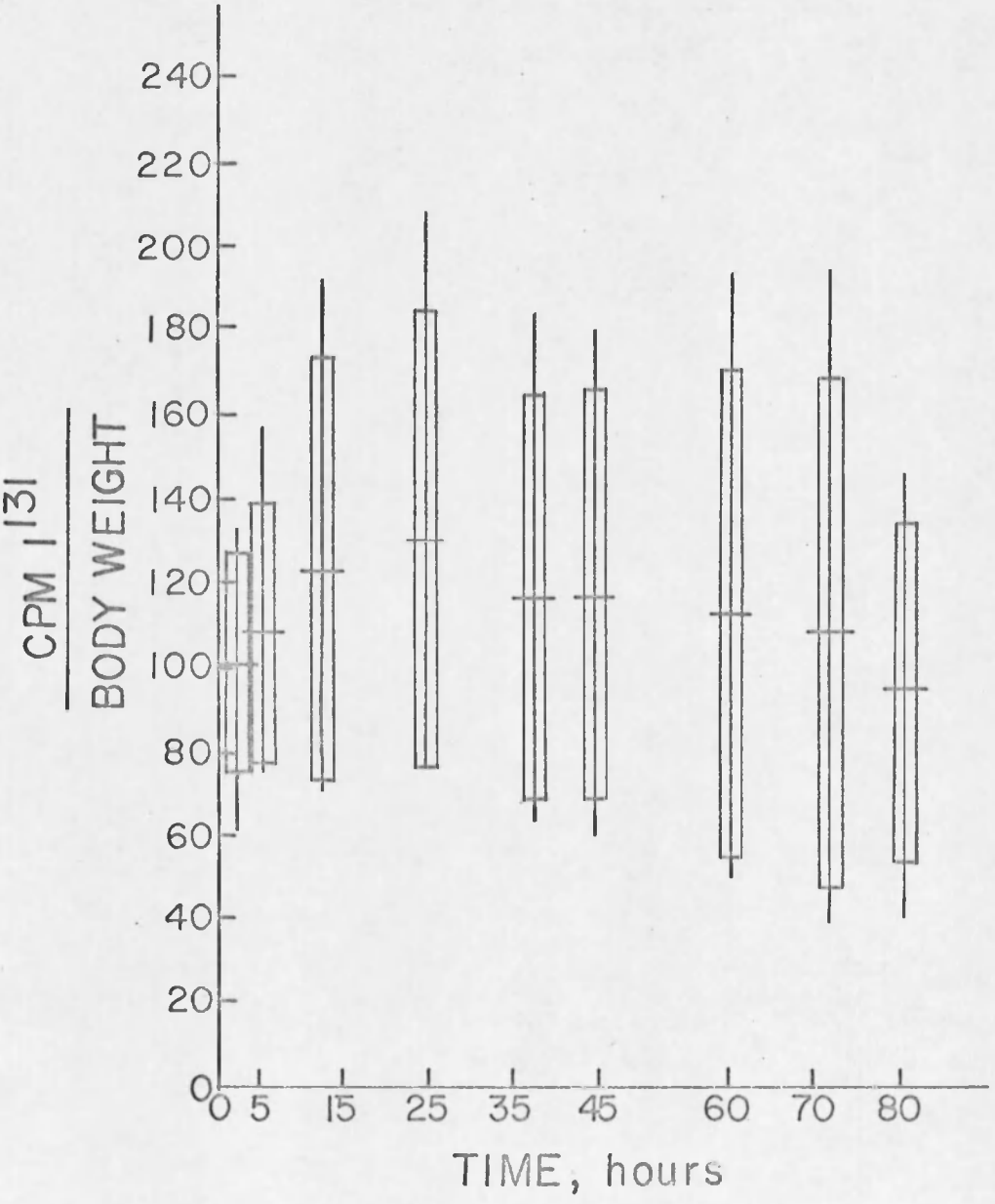

Figure 2. Mean thyroidal I^{131} uptake (± 2 standard deviations) of control ground squirrels.

Each point was determined from squirrels A through H (eight animals).

Figure 3. Stereodiagrams of the anterior right half of the ground squirrel brain.

Anterior hypothalamic lesions typically occurred within the stippled area. Abbreviations: A, anterior extent of anterior hypothalamus; B, posterior extent of anterior hypothalamus; CO, optic chiasma; FM, nucleus paraventricularis, pars magnocellularis; FP, nucleus paraventricularis, pars parvocellularis; HA, anterior hypothalamus; HL, lateral hypothalamus; HPV, nucleus periventricularis; NOM, nucleus preopticus medialis; SC, nucleus suprachiasmaticus; SO, nucleus supraopticus; TO, optic tract; VIII, third ventricle.

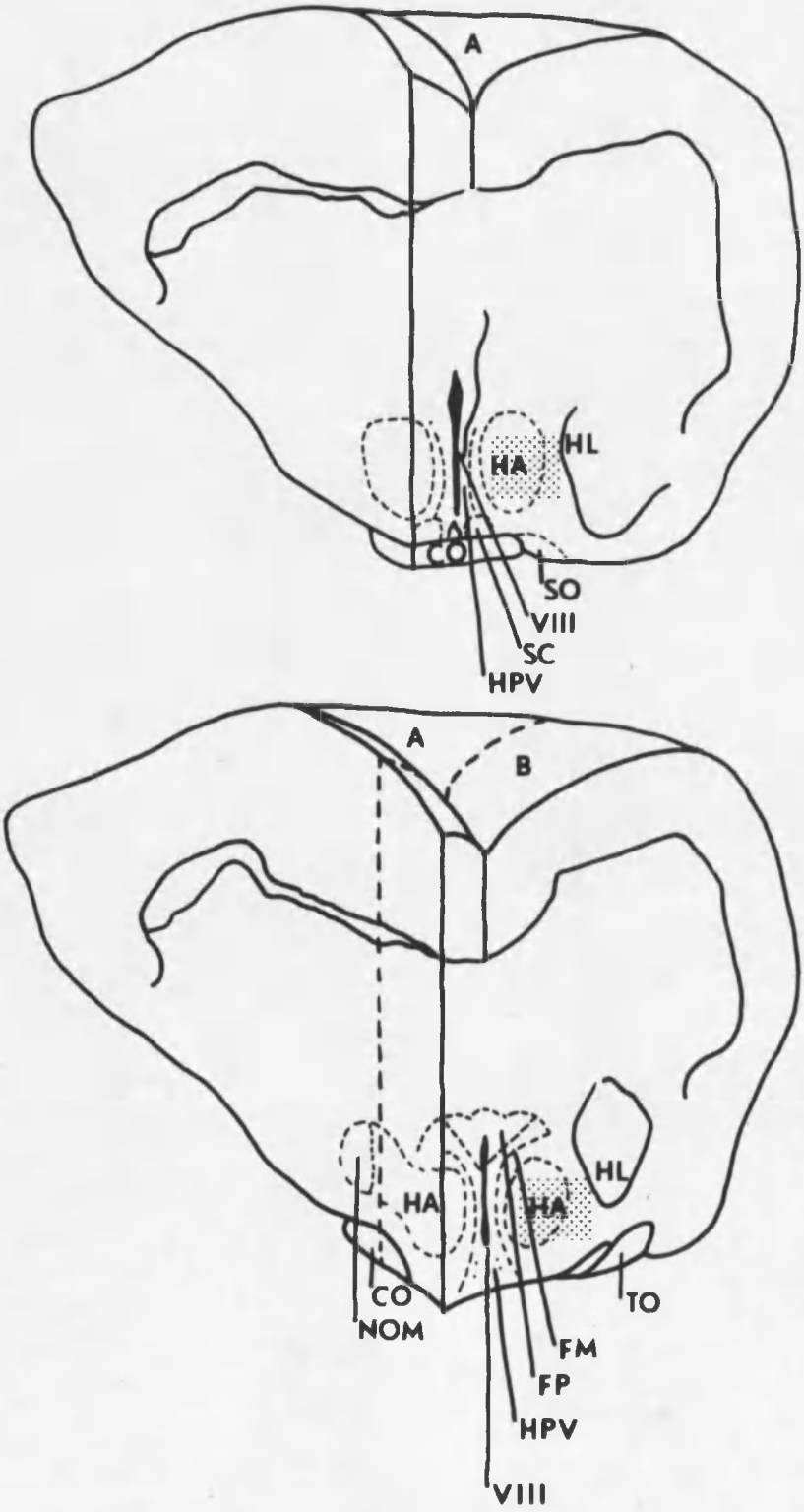

Figure 3. Stereodiagrams of the anterior right half of the ground squirrel brain.

generally damaged portions of the nucleus preopticus lateralis and nucleus preopticus medialis. Other nuclei were damaged in these squirrels, but the lesions did not extend posteriorly into the anterior hypothalamus.

The maximum activity of the thyroid glands of control squirrels varied as shown in Figure 4A. This distribution is probably the normal one for thyroid activity in squirrels at low ambient temperature and in hibernation. In Figure 4B, number of lesioned animals is plotted against maximum activity. It is significant here that squirrels 1 through 8 with anterior hypothalamic lesions are grouped below the normal distribution.

Control squirrels A through H and lesioned squirrels 9 through 14 have histologically normal-appearing thyroid glands (Figure 5). The follicular epithelial cells are cuboidal in shape and have a small amount of cytoplasm surrounding the nucleus. Relatively large areas of colloid with smooth outer edges are present in most follicles. The appearance of the thyroidal colloid from squirrels I and 15 is contained in smaller follicles than in the control squirrels, and light staining vacuoles occur at the periphery of the colloid. The most strikingly abnormal thyroids occur in squirrels 1 through 8 (Figure 6). The follicular cells of these thyroid glands are squamose with very little cytoplasm surrounding the nucleus. The

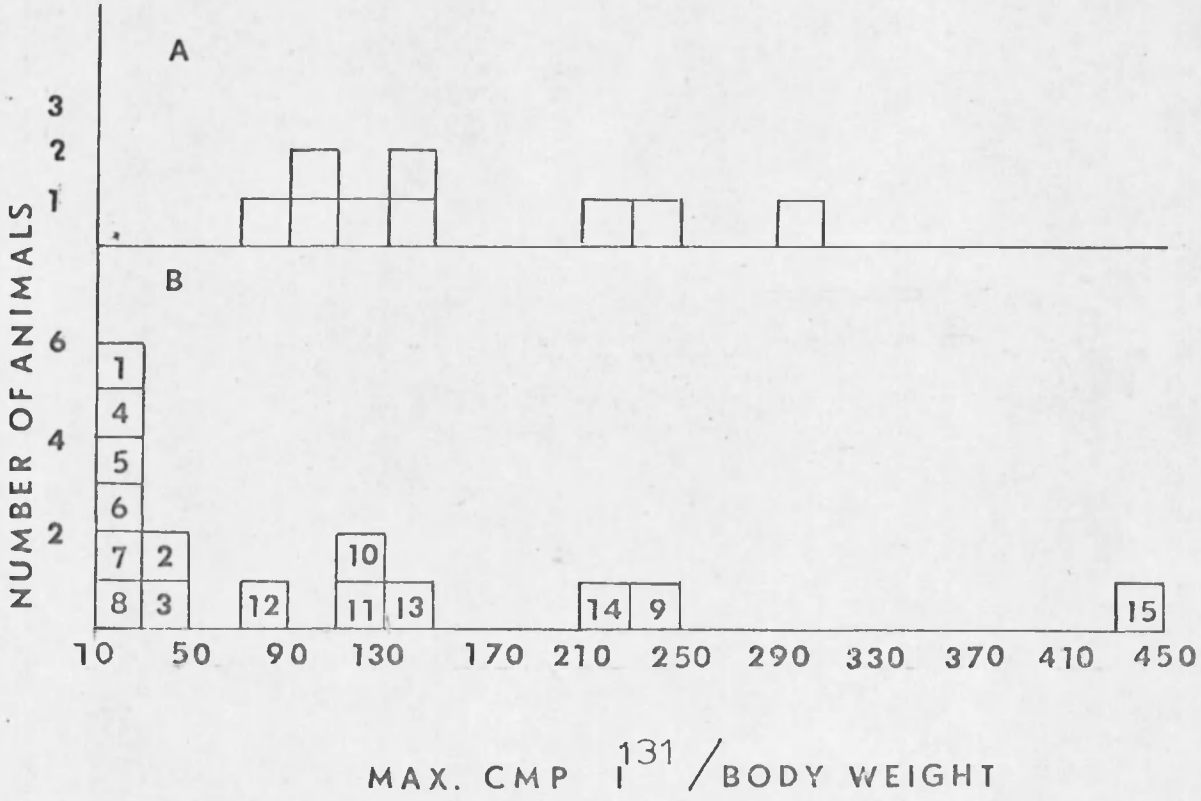

Figure 4. Distribution of lesioned and control ground squirrels as based upon maximum thyroidal I^{131} uptake.

A. Control squirrels. This is probably the normal distribution for thyroid activity in ground squirrels.
B. Lesioned squirrels. Numbers correspond to squirrels and lesion locations given in Figure 1.

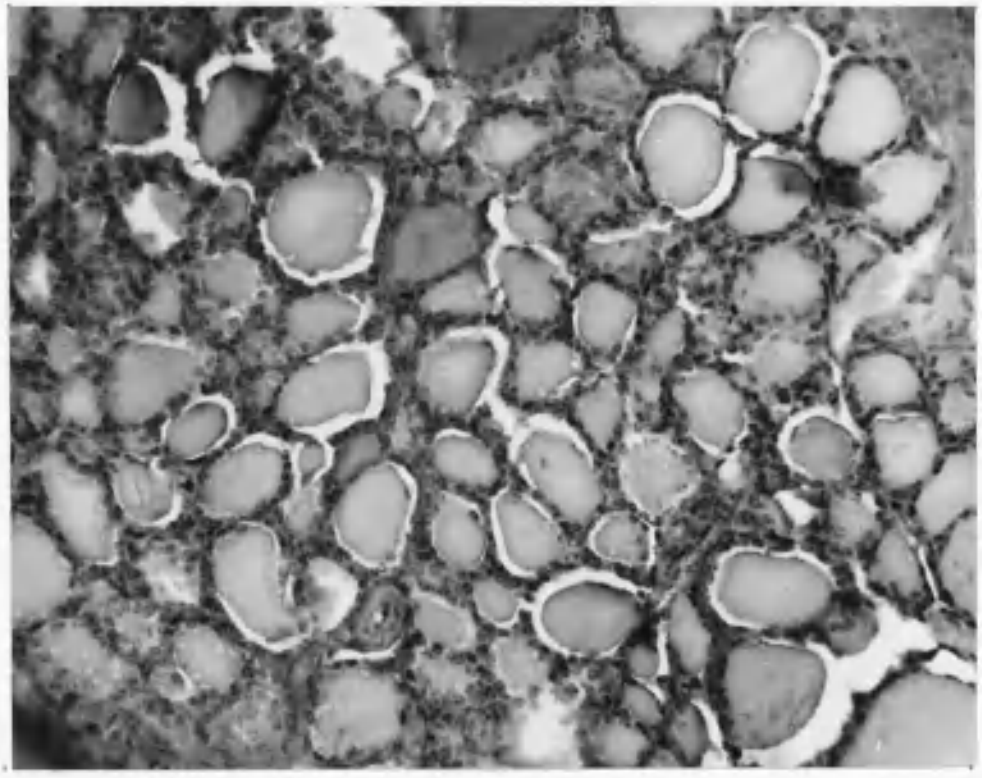

Figure 5. Cross section through a thyroid gland from a lesioned ground squirrel without anterior hypothalamic damage.

This histological appearance was also typical of control squirrels.

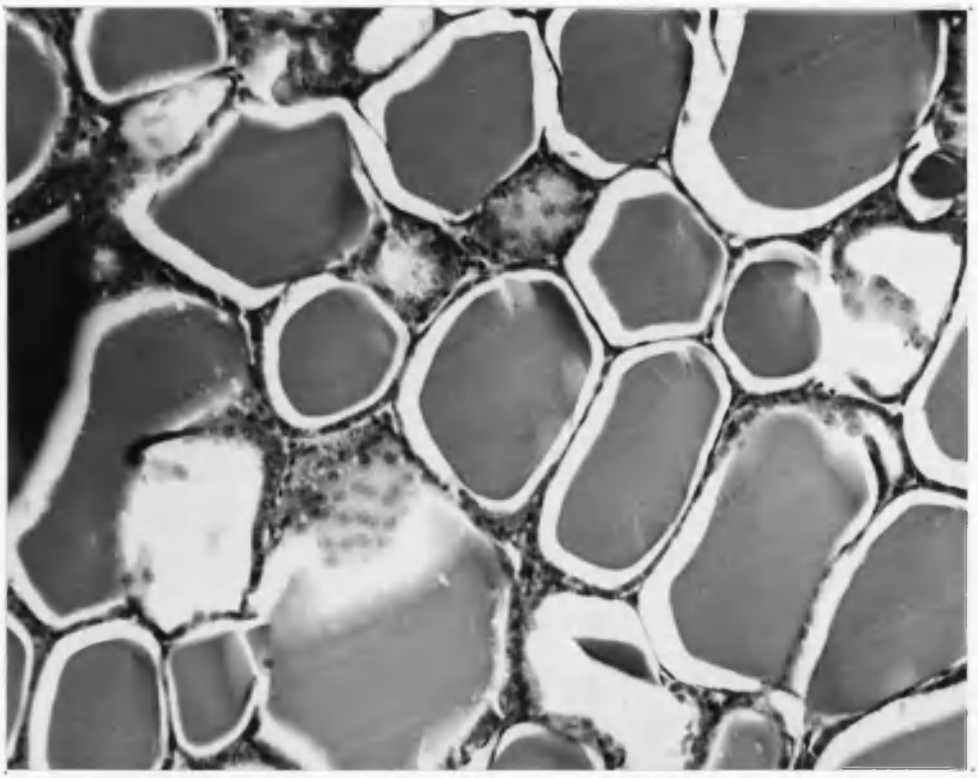

Figure 6. Cross section through a thyroid gland from a ground squirrel with an anterior hypothalamic lesion.

follicles contain large amounts of colloid and appear to stain more densely than those of the other squirrels.

Body temperatures were recorded at various intervals during the investigation, and the results are presented in Table 2. With only two exceptions the squirrels without anterior hypothalamic lesions either maintained body temperatures around 29°C, or their body temperatures fluctuated from 32°C to 6°C. Although the body temperatures of these squirrels dropped to extremely low levels, they maintained these low temperatures for only short periods of time. Squirrels with anterior hypothalamic lesions had body temperatures of 6°C to 8°C. The mean body temperatures (± 2 standard deviations) for the lesioned squirrels and the controls are presented in Figures 7, 8, and 9.

Table 2. Body temperature response of control and lesioned ground squirrels to reductions in ambient temperatures.

	Days in environmental chamber						
	3	7	13	14	15	16	17
	Ambient temperature (°C)						
	19	13	5	5	5	5	5
Lesioned Squirrels	Body Temperature (°C)						
1	25	13	8	+			
2	19	13	8	8	+		
3	28	25	7	+			
4	27	23	6	+			
5	31	31	8	+			
6	19	12	7	+			
7	30	12	7	+			
8	31	29	7	+			
9	33	20	7	+			
10	26	17	23	19	12	8	*
11	20	29	27	33	6	18	*
12	19	13	9	18	7	8	*
13	30	27	7	7	+		
14	31	31	28	32	30	27	*
15	29	12	8	29	17	29	*
Controls							
A			28	30	30	28	28
B			30	30	14	28	6
C			9	8	30	6	8
D			29	30	30	27	30
E			27	15	25	25	26
F			28	7	28	7	7
G			28	30	28	30	28
H			8	8	30	7	29
I			30	15	31	26	19

\+ Died during investigation.

* Sacrificed.

1 through 8 had anterior hypothalamic lesions; 9 through 15 were sham lesioned squirrels.

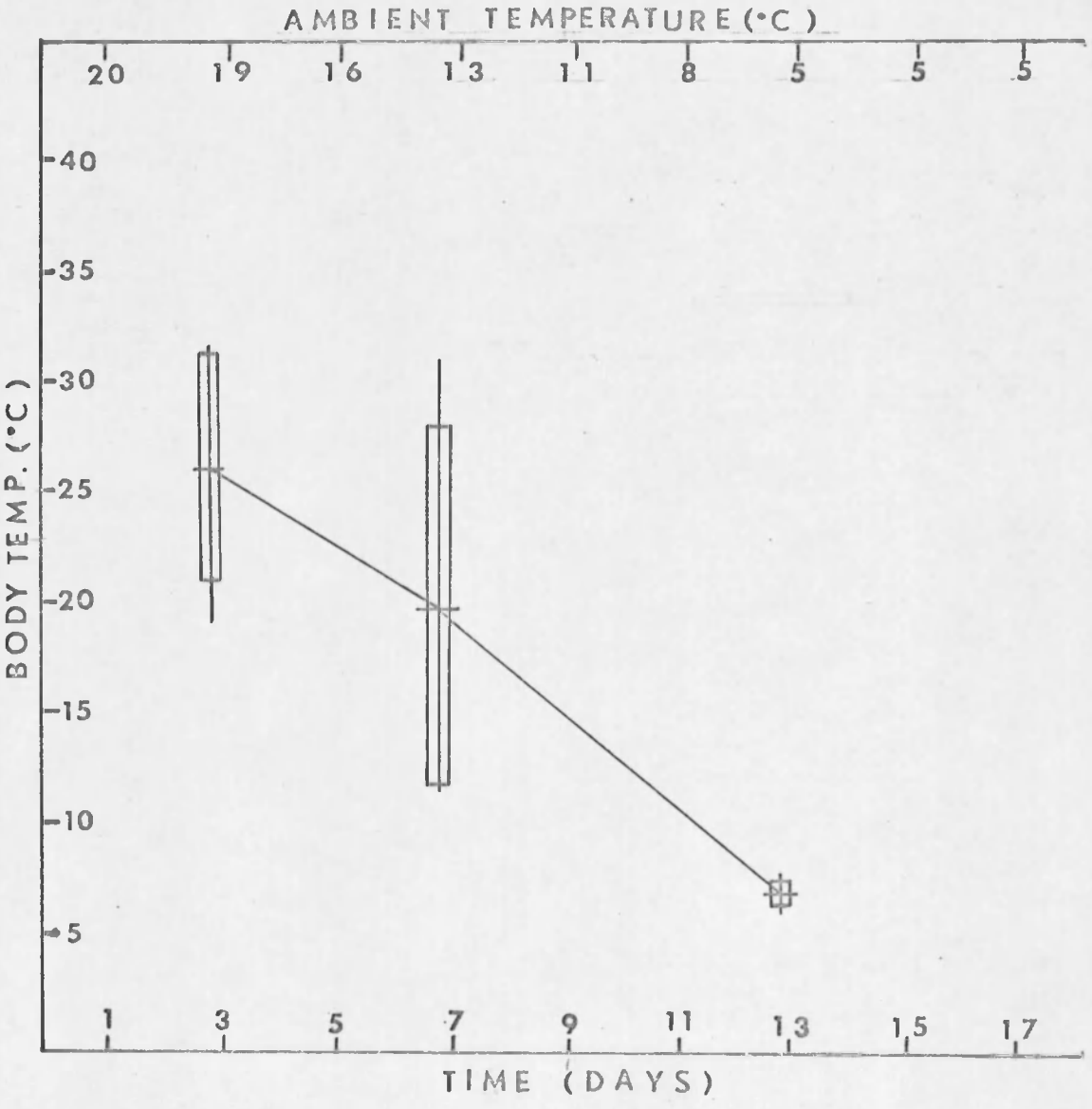

Figure 7. Mean body temperature response (± 2 standard deviations) of ground squirrels with anterior hypothalamic lesions to reductions in ambient temperature (N=8).

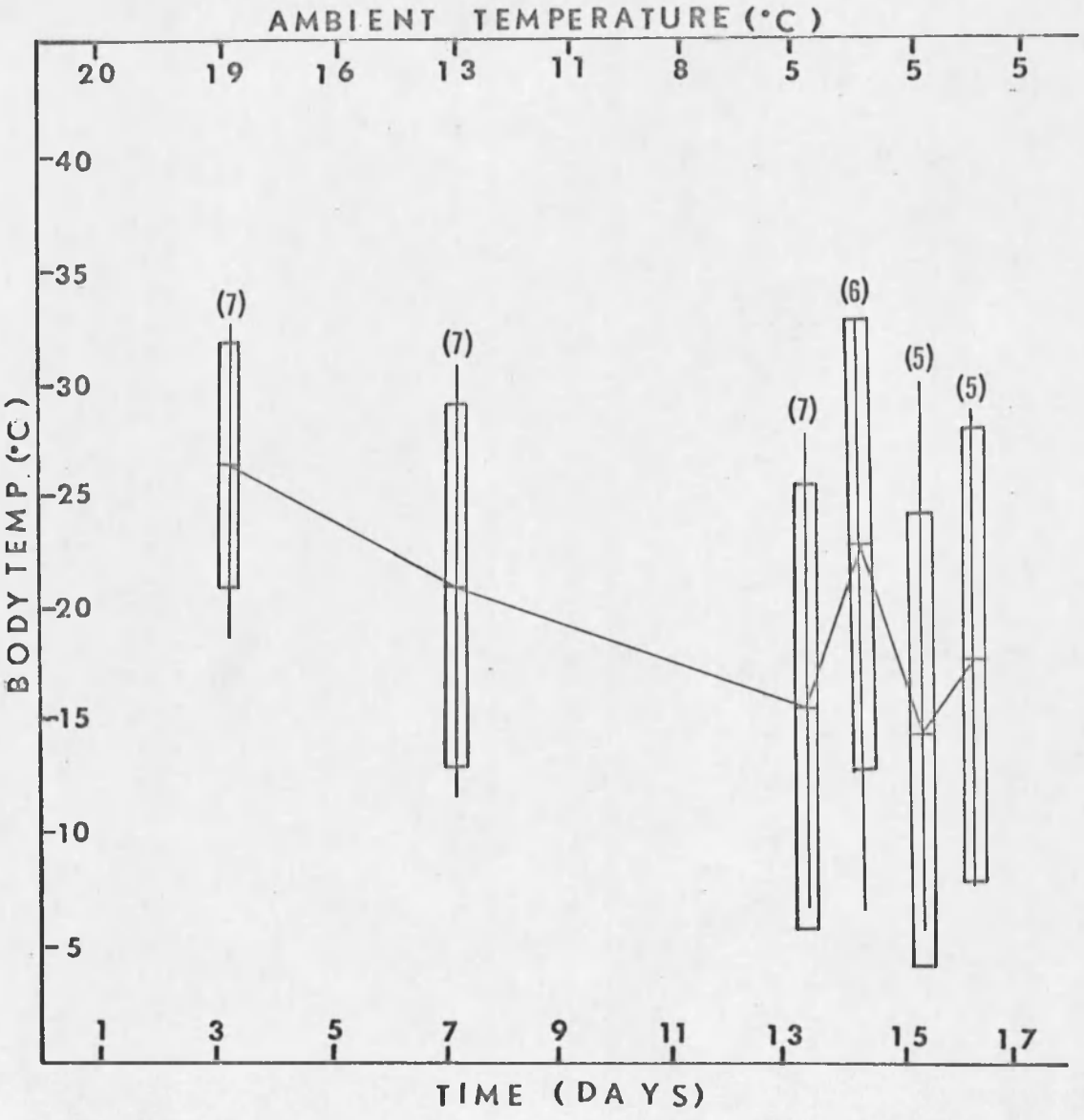

Figure 8. Mean body temperature response (± 2 standard deviations) of lesioned ground squirrels without anterior hypothalamic damage to reductions in ambient temperature.

Numbers in parenthesis represent the n number of squirrels.

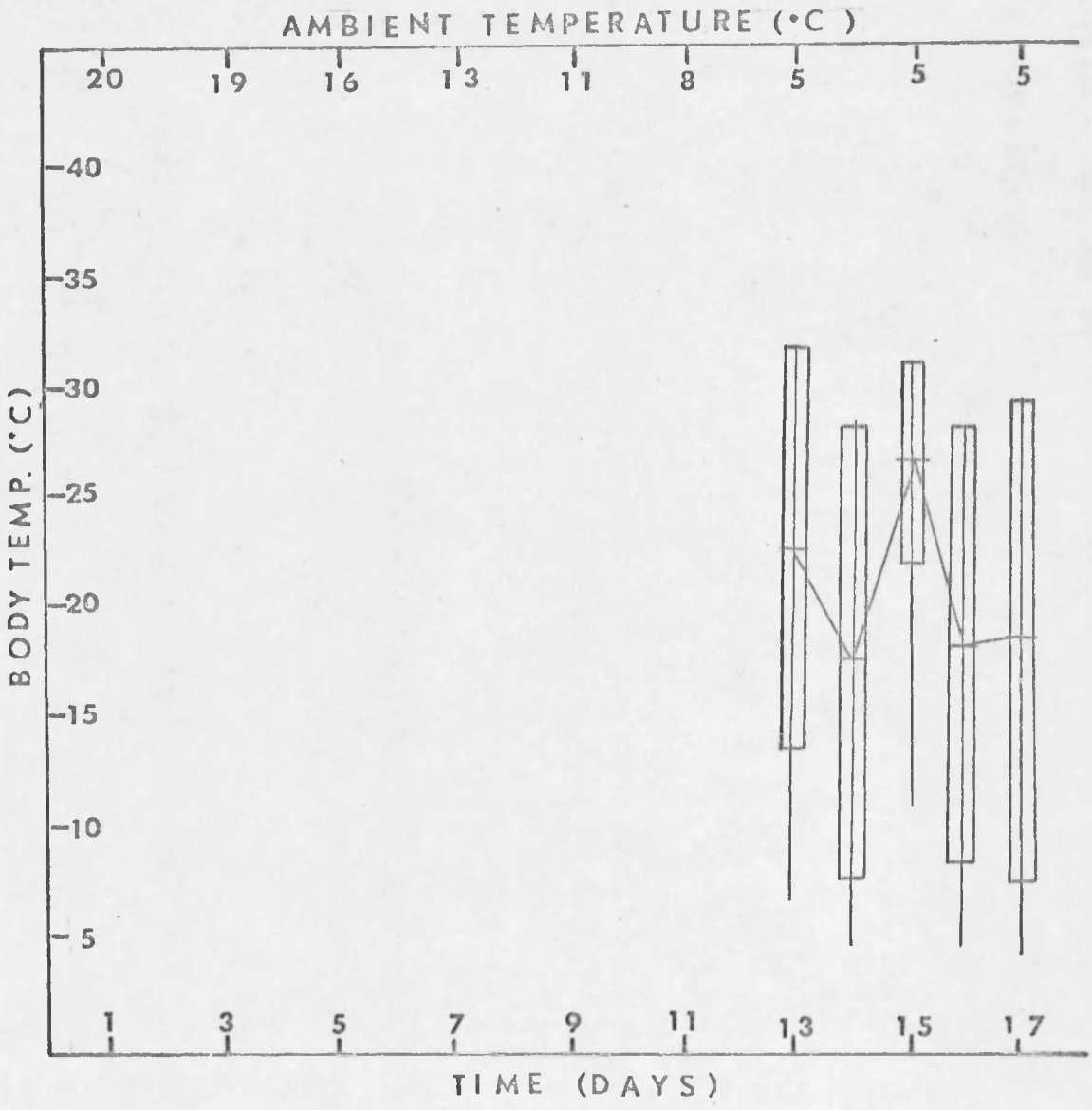

Figure 9. Mean body temperature response (± 2 standard deviations) of control ground squirrels to reductions in ambient temperature (N=9).

DISCUSSION

Knigge and Bierman (1958) have shown that median eminence lesions inhibit thyroid I^{131} release in hamsters placed in the cold (5°C). Since the median eminence is a common pathway for many hypothalamic releasing factors, this observation does not give insight regarding thyroid control by a specific hypothalamic region in hibernators. Averill and Salaman (1967) have observed that electrical stimulation of the anterior hypothalamus of the rabbit significantly increases TSH concentration in peripheral blood. These investigators have also noticed that transplanting the pituitary gland to an area removed from the hypothalamus prevents activation of the thyroid gland by cold exposure or by electrical stimulation. D'Angelo (1963) has reported that guinea pigs lesioned bilaterally in the preoptic and anterior hypothalamus and then exposed to cold (5°C) exhibited reduced pituitary weight, inhibited thyroid activation and reduced circulating TSH titers. These observations indicate that the anterior hypothalamus is influential in regulating thyroid activity. Stimulation of the preoptic and anterior hypothalamus activates the thyroid in various non-hibernating mammals, and destruction

of these areas inhibits thyroid activity (Averill and Salaman, 1967; D'Angelo, 1963).

The results of the present investigation agree with the findings of Knigge and Bierman (1958) in that partial or total destruction of the anterior hypothalami of hibernating ground squirrels placed in the cold (5°C) causes a significant decrease in thyroid activity. Apparently the anterior hypothalamus of the ground squirrel and that of the non-hibernator (D'Angelo, 1963) have similar roles in thyroid activity. These findings are in opposition to the hypothesis that the hypothalamus actively inhibits thyroid activity in hibernators (Suomalainen and Nyholm, 1956; Petrovic and Kayser, 1958).

The histological appearance of the thyroid glands of ground squirrels without anterior hypothalamic lesions and glands of control ground squirrels appeared normal and did not show signs of activation due to low ambient temperatures. This result parallels previous histological observations of golden hamster thyroid glands (Tashima, 1965). Uptakes of I^{131} by the thyroid glands of control and of non-anterior-hypothalamic-lesioned squirrels were nearly equal. No explanation can be given for the high I^{131} uptake by the thyroid glands of control squirrel I or of lesioned squirrel 15.

In their investigation of hamsters, Knigge and Bierman (1958) reported that hypothalamic lesioning often resulted in an inability of the hamster to maintain normal body temperature when placed in the cold. Recently, Satinoff (1967a) observed that hypothermic (14-20°C) ground squirrels with anterior hypothalamic lesions required a 2 to 6 times greater time interval to regain normal body temperature at 10°C ambient temperature than did control animals. When ground squirrels with anterior hypothalamic lesions were exposed to 5°C ambient temperature (Satinoff, 1967b), hypothermic and hibernating squirrels died without regaining normal body temperature or arousing from hibernation.

During this investigation, behavior paralleling the previously mentioned observations was seen. At a 5°C ambient temperature, ground squirrels with anterior hypothalamic lesions permanently reduced their body temperatures to 6°C or 8°C. Ground squirrels without anterior hypothalamic lesions and non-lesioned control squirrels either maintained their body temperatures at approximately 29°C or exhibited fluctuations in body temperature from 32°C to 6°C. Brain temperatures of hibernating ground squirrels have shown similar fluctuations at reduced ambient temperatures (Strumwasser, 1959).

The data presented in this investigation suggest that lesions in the anterior hypothalamus of Citellus tereticaudus result in decreased thyroid I^{131} uptake at $5^{o}C$ ambient temperature. This conclusion is supported by observed reduction in body temperature, inability of the squirrel to occasionally elevate its body temperature, and finally the death of the animal.

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