in March and July. However, agreement with all the parameters utilized was not obtained.

Summary. Thyroid gland activity as measured by percent colloid, cell height, I^{131} uptake and thyroxine secretion rates was studied in 2 subspecies of male deermice (*P. m. bairdii* and *P. m. gracilis*) during spring, summer, fall and winter. A seasonal difference in activity of the thyroid gland was noted in both subspecies. However, time of maximum and minimum activity also varies in the 2 subspecies. Thyroid cell height and TSR are at a maximum during December-March and a minimum in October for *bairdii,* and are at a maximum during October-December and a minimum during March-July for *gracilis*. Radioiodine uptake by the thyroid glands of both subspecies is high during July and December and low during March and October. With the exception of the October period, the thyroid gland of *bairdii* is more active throughout the year than the thyroid of *gracilis*. A lack of agreement with all parameters of thyroid activity utilized was noted.

1. Hunt, R., *Am. J. Physiol.,* 1923, v63, 257.
2. Coninx-Girardet, B., *Acta Zool.,* 1927, v8, 161.
3. Zalesky, M., *Anat. Rec.,* 1935, v62, 109.
4. Tala, P., *Acta Endocrinol.,* 1940, Suppl. 9.
5. Kayser, C., *Imprimerie M. Declume,* 1940, 1.
6. Adams, A. E., *Quart. Rev. Biol.,* 1946, v21, 1.
7. Hoffman, R. A., Zarrow, M. X., *Acta Endocrinol.,* 1958, v27, 77.
8. King, J. A., *J. Mamm.,* 1958, v39, 177.
9. King, J. A., Eleftheriou, B. E., *J. Comp. Physiol. Psych.,* 1959, v52, 82.
10. Eleftheriou, B. E., 1961, Ph.D. Thesis, Purdue Univ.
11. Uotila, U., Kannas, O., *Acta Endocrinol.,* 1952, v11, 49.
12. Purves, H. D., Griesbach, W. E., *Endocrinol.,* 1951, v49, 652.
13. Grosvenor, C. E., Turner, C. W., PROC. SOC. EXP. BIOL. AND MED., 1958, v99, 517.

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Blood Glucose Changes Induced by Cold, Epinephrine, and Norepinephrine in Dogs of Various Ages.* (27445)

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In experiments concerning the development of temperature regulation in newborn dogs it was observed that prior to 10 days of age the animals did not show much increase in metabolic rate on exposure to cold(1,2). This finding suggested that the newborn may have deficient chemical means of increasing the metabolic rate in response to cold. The incomplete state of development of the sympathetic-adrenal-hypothalamic system in the newborn may also explain the inadequate response to the cold environment(3). The experiments described below were done in an attempt to find if the glycemic response to cold, epinephrine, or norepinephrine varied with age in the dog, and might be related to the development of homeothermy.

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Methods. The animals used were healthy mongrel dogs of both sexes which were kept in air-conditioned kennels at approximately 22°C. In a typical procedure the adult animal was not fed for 12 hours prior to drawing blood for glucose determination. Nursing pups were kept with the female until just before blood sampling, and therefore were not in a fasting state. Blood glucose was determined on 0.1 ml samples of blood drawn from a leg vein, ear, or from a cardiac puncture sample, using the Nelson-Somogyi method(4). Immediately after the control sample, rectal temperature was taken with a thermocouple, and one of the following experimental conditions was imposed: (a) saline, 0.2 ml/kg; (b) epinephrine, 0.2 mg/kg; (c) norepinephrine, 0.2 mg/kg.

Following the intramuscular injections, ani-

TABLE I. Control Blood Glucose Level in Dogs of Various Ages.

	Age in days						
	1–4	5–7	8–10	11–15	16–20	21–25	Adult
Blood glucose (mg %)	97	96	106	114	110	110	67
No. of samples	81	54	85	78	61	70	58
Stand. dev.	29	22	21	22	21	18	14

TABLE II. Change in Blood Glucose after Experimental Procedures (mg %).

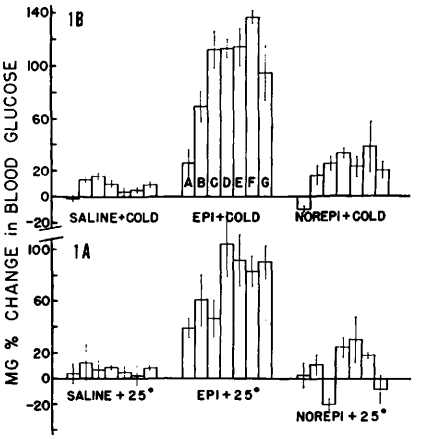
Procedure	Air temp., °C	Age in days							No. of trials
		1–4	5–7	8–10	11–15	16–20	21–25	Adult	
Saline	25	+ 3	+11	+ 6	+ 8	+ 4	+ 1	+ 7	58
"	4	- 1	+13	+ 16	+ 10	+ 4	+ 5	+ 9	189
Epi.	25	+39	+60	+ 45	+103	+ 91	+ 82	+85	49
"	4	+26	+68	+112	+113	+114	+136	+94	74
Norepi.	25	+ 3	+10	- 21	+ 23	+ 29	+ 17	- 9	49
"	4	- 10	+16	+ 25	+ 33	+ 23	+ 38	+20	64

mals were exposed to an air temperature of 25°C (± 2°), or to 4°C (± 2°) for one hr. During cold exposure the animals were confined to a wooden cage that permitted free movement, but not running or jumping. At the end of this time a blood sample and rectal temperature reading were taken.

Results. Data were grouped into age categories of 1-4, 5-7, 8-10, 11-15, 16-20, 21-25 days, and adults, to facilitate graphing and statistical analysis. Tables I and II show the average responses found in various age groups when dogs were subjected to the experimental conditions described. Fig. 1A compares blood glucose responses of the several age groups in the cold room and Fig. 1B compares changes observed at 25°C.

At ages 1-25 days dogs had higher control blood glucose levels ($P = 0.01$), but considerably greater variation, than did adult dogs, as indicated by the mean values and standard deviations in Table I. In part, this difference may have been due to the 12-hour fast imposed on the adults, but not on the pups, prior to blood sampling.

The control saline injection resulted in little change in blood glucose in any of the animals (Fig. 1A and Table II). When cold-exposed, the animals 4 days or younger had a fall in blood glucose, whereas the older animals had a rise in glucose (Fig. 1B and Table II). Epinephrine injection produced a hyperglycemic response in all dogs, but in the 1-4-



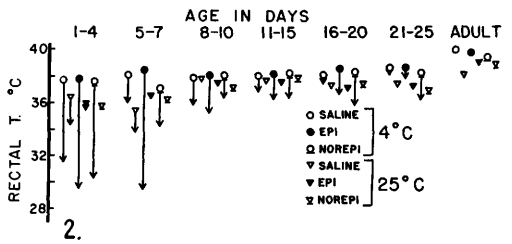


FIG. 1. A. Effect of saline, epinephrine, or norepinephrine inj., followed by cold exposure (4°C), on blood glucose. Bars represent age in days as follows: A, 1-4; B, 5-7; C, 8-10; D, 11-15; E, 16-20; F, 21-25; G, adults. Unmarked bars are in the same order. Base line is control blood glucose level. Stand. error of mean is indicated by single line in each bar. B. Animals were inj. as in A, but were not cold exposed (25°C). Age groups are same as labeled bars in A. Stand. error of mean indicated by single line in each bar.

FIG. 2. Rectal temperature changes in dogs given saline, epinephrine, or norepinephrine, and exposed to 4°C, or 25°C air for 1 hr.

day group the response was considerably less than in the older groups (Fig. 1A and Table II). Cold exposure combined with epinephrine injection gave a greater rise in blood glucose than either of these procedures alone in all groups except 1-4-day dogs. These had less hyperglycemic response to cold plus epinephrine than older pups and adults (Fig. 1B and Table II). The results indicated in general that in response to cold, epinephrine injection, or epinephrine plus cold exposure, the dogs 4 days or younger had a significantly lower hyperglycemic response than did older pups or adults ($P = <0.05$).

Norepinephrine gave variable glycemic responses in all age groups, with no difference attributable to age of the animals (Fig. 1A and Table II). When cold exposure and norepinephrine were combined, a hyperglycemic effect was found in all dogs over 4 days of age, but in animals younger than this there was a hypoglycemic response (Fig. 1B and Table II). This result was significantly different from that in older pups and adults ($P = <0.01$). In animals above 4 days of age the combination of cold and norepinephrine gave a slightly greater and more consistent hyperglycemia than did norepinephrine alone (Fig. 1A & B).

The normal rectal temperatures of pups aged 1-25 days tended to be lower and more variable than in adult dogs (Fig. 2). There was a gradual rise in temperature with age, and at 25 days not much variation from the adult level was found. On cold exposure for one hour the temperatures of dogs under 10 days fell sharply, the greatest fall occurring in the youngest animals. With age, the temperature fell less, indicating that development of thermoregulation extended over a period of 3-4 weeks.

In animals under 8 days of age administration of epinephrine prior to cold exposure resulted in a greater fall in rectal temperature than when saline was given ($P = <0.05$). This was not observed with norepinephrine ($P = > 0.1$) nor in the animals older than 8 days.

Discussion. The development of homeothermy undoubtedly involves the gradual maturing of several calorigenic processes by which heat is produced through chemical and physical means. Our previous studies on newborn dogs revealed that they failed to respond to cold exposure with sufficient increases in metabolic rate to maintain a normal body temperature until the age of 3-4 weeks(1,2). The poor cold resistance appeared to be due to the relatively weak shivering movements, and to the low chemical heat production of the newborn animal.

Blood glucose and liver glycogen levels of newborn animals and human infants have been found to be near adult levels, but highly variable in the first few days postpartum(5, 6,7,8). This was also true of the newborn dogs, in which blood glucose levels were found significantly higher, but considerably more variable than in adult dogs used in our experiments (Table I). In part this may be explained by the 12-hour fasting period applied to the adults before sampling, a condition found not practical to impose on the immature animals. However, adult blood glucose data reported by others for dogs are also highly variable, possibly because of the variety of physiological and psychological conditions which accompanied the sampling(9, 10).

The reported results of cold exposure on the blood glucose level of adult animals and man are not entirely in agreement. Past experimenters have found a fall, no change, or more frequently a rise in glucose(11). Again, the experimental conditions varied sufficiently to explain the discrepancies. Some data on the glycemic responses of newborn pigs exposed to cold have been reported, but very little information appears to have been published for the newborn dog(6,12). From the data presented above it is apparent that cold exposure did not induce a hyperglycemic response in the youngest age group (1-4 days), but did so in the older animals and adults. The lack of glycemic response may be related to the underdevelopment of the sympathetic-adrenal-hypothalamic system at this age. This is suggested by experiments in adult dogs in which it was found that adrenal demedullation or adrenergic blockade prevented the usual hyperglycemic response observed on cold exposure(13). Lack of carbohydrate stores does not appear to be a limiting factor, since liver glycogen has been found high at

birth(14), and glucose-6-phosphatase activity present(15). A rapid drop in liver glycogen soon after birth has been reported in several species of animals, indicating that this is one readily available source of energy (14).

The hyperglycemic response of the youngest group of animals following epinephrine was considerably below that of older dogs, but its consistent occurrence indicated that some carbohydrate stores were available at this age. Similar results have been reported for newborn human infants, who also show an increase in the hyperglycemic response with age resembling that found in the dog (16). When cold exposure was added to epinephrine injection, all but the youngest group of dogs showed greater hyperglycemia than that produced by either of these stimuli alone. In this procedure the 2 youngest groups showed sharp drops in rectal temperature, but nevertheless the hyperglycemic response in the 5-7-day-olds was almost equal to that seen at 25°C, indicating that enzyme inhibition by cold did not appreciably limit the response, as suggested by some workers (6).

Norepinephrine had small and variable effects on blood glucose, which also have been the findings of others(17). When norepinephrine and cold were additive a somewhat greater and more consistent hyperglycemia was found, except in the youngest group of animals, which showed a fall in blood glucose that further substantiated the inadequacy of calorigenic responses at this stage of development.

In immature animals the control rectal temperature showed a gradual upward trend with age, and the rise in resistance to cold paralleled this. In dogs under 8 days the epinephrine-treated group cooled more than the saline-treated group, suggesting a detrimental effect of this amine, rather than a calorigenic one. Essex(18) found a similar response in small adult dogs given large amounts of epinephrine in ordinary room temperatures. In none of the age groups studied did the metabolic stimulation attributed to the amines appear to give increased resistance to cold as indicated by rectal temperature changes.

Summary. Under the age of 5 days newborn dogs did not have a hyperglycemic response to cold exposure for one hour, while pups older than this, as well as adults, showed a significant rise in blood glucose. Epinephrine alone or combined with cold exposure produced a hyperglycemic effect in dogs of all ages, but the response was considerably lower in dogs under 5 days. Norepinephrine had a small and variable effect on blood glucose. The combination of norepinephrine with cold gave a somewhat larger and more consistent hyperglycemia, except in the youngest dogs, which had a hypoglycemic response. Dogs under 8 days had greater depression of rectal temperature in the cold after epinephrine than after saline or norepinephrine administration. In none of the animals did the calorigenic effects of the amines increase cold resistance, as indicated by rectal temperature changes.

1. Jensen, C., Ederstrom, H. E., *Am. J. Physiol.*, 1955, v183, 340.

2. McIntyre, D. G., Ederstrom, H. E., *ibid.*, 1958, v194, 293.

3. Adolph, E. F., *Quart. Rev. Biol.*, 1957 v32, 89.

4. Reiner, M., (Editor) *Standard Methods of Clinical Chemistry*, Academic Press, Inc., N. Y., 1953, v6, p65.

5. Britton, S. W., *Am. J. Physiol.*, 1930, v95, 178.

6. McCance, R. A., Widdowson, E. M., *J. Physiol.*, 1959, v147, 124.

7. Goodwin, R. F. W., *ibid.*, 1957, v136, 208.

8. Norval, M. A., Kennedy, R. L. J., Berkson, J., *J. Pediat.*, 1949, v34, 342.

9. Kramer, B., Coffin, H. W., *J. Biol. Chem.*, 1925, v25, 423.

10. Foa, P., Weinstein, H. R., Smith, J. A., *Am. J. Physiol.*, 1949, v157, 197.

11. Burton, A. C., Edholm, O. G., *Man in a Cold Environment*, Edward Arnold Pub., Ltd., London, 1955, p214.

12. Schlossman, H., *J. Physiol.*, 1938, v92, 219.

13. Kilburn, K. H., *Am. J. Physiol.*, 1960, v199, 955.

14. Shelley, H. J., *Brit. Med. Bull.*, 1961, v17, 137.

15. Weber, G., Cantero, A., *Cancer Res.*, 1957, v17, 995.

16. Desmond, M. M., *J. Pediat.*, 1953, v43, 253.

17. Von Euler, U. S., *Noradrenaline*, C. C Thomas, Springfield, Ill., 1956, p214.

18. Essex, H. E., *Am. J. Physiol.*, 1952, v171, 78.

Received February 15, 1962. P.S.E.B.M., 1962, v110.