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THE ROLE OF THE THYROID IN RATS EXPOSED TO COLD

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The close correlation between increased thyroid activity and increased heat production on the one hand and exposure to cold on the other has led to the belief that increased thyroid activity is the mechanism by which increased heat production is brought about in animals exposed to cold. This belief has been strengthened by similarities between the behaviour *in vitro* of tissues of hyperthyroid and of cold-adapted animals (Weiss, 1957; Smith, 1960). Food selection (Donhoffer & Vonotzky, 1947*a*, *b*) and food absorption (Hsieh & Ti, 1960) of the animals are also comparable. But if thyroid hormone is the mediator for increased heat production in cold-exposed animals one would expect to find either increased plasma concentration of the hormone or increased sensitivity of the tissues to the hormone.

Experiments on the sensitivity of the tissues of cold-adapted rats to thyroid hormone have not been performed. However, Sellers & You (1950) found that rats fed on a diet containing propylthiouracil lived but a few days when exposed to cold, while those animals given the anti-thyroid diet after several weeks of cold exposure survived 3–5 weeks. This can be interpreted as indicating that the requirement for thyroid hormone becomes less as the animals become adapted to cold. The main objection to this hypothesis is the use of a commercial diet in the experiments. The experiments of Leblond & Eartly (1952) and Gemmill (1958) suggest that the iodine in commercial laboratory food is in a hormonally active form. Since the daily food consumption of rats exposed to cold increases with time, the increased amounts of active iodine present in the commercial diet ingested by cold-exposed rats may be responsible for the prolonged survival time when a thyroid gland blocking agent is added. Another point that does not seem to have received attention is the physical condition of the animals at the beginning of the experiment. In one case the animals have a low metabolic rate, low food intake and myxoedematous hearts; in the other the low environmental temperature has already induced compensatory changes.

Plasma protein-bound-iodine concentrations are not increased in cold-exposed rats (Rand, Riggs & Talbot, 1952), guinea-pigs (Stevens, D'Angelo, Pashkis, Cantarow & Sunderman, 1955), sheep (Freinkel & Lewis, 1957)

and man (Ingbar & Bass, 1957). Adaptation to cold does not depend upon a hyperthyroid state (Sellers & You, 1950). Thus it is possible that the thyroid gland is merely responding to a situation in which there is increased utilization of thyroid hormone.

A study of some of the factors that affect survival of hypothyroid rats in the cold would aid in determining the role of the thyroid gland in the metabolic response to cold. The present paper gives the results of an investigation into the effects on the survival time of male albino rats living at 4° C and fed on a diet containing 0·05 % propylthiouracil (1) of the nature of the basal diet, (2) of previous exposure to cold, (3) of the degree of thyroid hormone depletion and (4) of the amount of thyroid hormone given as replacement.

METHODS

Male albino rats of approximately the same age and weighing about 220 g at the beginning of the experiments were kept in individual metal cages and given food and water *ad libitum*. During control periods the animals were kept in a room maintained at about 28° C; exposure to cold was obtained by transferring the cages to another room maintained at about 4° C. Body weights were recorded each morning at about the same hour. Survival time was estimated to the nearest day.

Two basal diets were used: (1) Purina Laboratory Chow (Ralston Purina) in powdered form and, (2) an iodine-deficient diet consisting of 70 % corn meal, 18 % wheat gluten, 10 % brewer's yeast, 1 % NaCl and 1 % $CaCO_3$ (Leblond & Eartly, 1952). Rats fed on the iodine-deficient diet were given water containing KI 4 μg/ml. to drink. Anti-thyroid diets contained 0·05 % propylthiouracil (Eli Lilly) and are referred to as commercial-PTU and iodine-deficient-PTU diets.

Rats on thyroid hormone replacement received daily subcutaneous injections of either L-thyroxine sodium (British Drug Houses) or 3:5:3′-triiodo-L-thyronine sodium (California Corporation for Biochemical Research). The hormones were dissolved in alkalinized water and concentrations adjusted so that the required doses were contained in 0·5 ml. of fluid. Control animals received injections of 0·5 ml. of alkalinized water.

Oxygen consumption was determined by a closed-circuit method. Rats were placed in individual plastic cylinders which were immersed in a water-bath maintained at 28° C. Air was circulated through towers containing soda-lime at a rate of about 2 l./min by modified aquarium pumps, and oxygen consumed was replaced from calibrated spirometers. The change in volume of the spirometers, representing oxygen consumption, could be read to 2·2 ml. This resulted in a 'reading error' of about 1·5 % when oxygen consumption was calculated for a 30 min period.

RESULTS

Preliminary experiments

As the animals were to be fed on the iodine-deficient-PTU diet for a relatively long period of time it was necessary to see if any deleterious effects not ascribable to lack of thyroid function would occur. Two experiments were performed for this purpose, oxygen consumption and body weights of rats kept at 28° C being used as criteria of the general condition of the animals.

Cross-over experiments. Six rats were divided into two groups of three each. One group was fed on iodine-deficient-PTU diet and the other on iodine-deficient diet. After 3 weeks the diets were exchanged. The results (Fig. 1) show the expected reduction in oxygen consumption and body weights of rats given PTU in the diet. Removal of the PTU in the diet was followed by recovery in rates of oxygen consumption and growth.

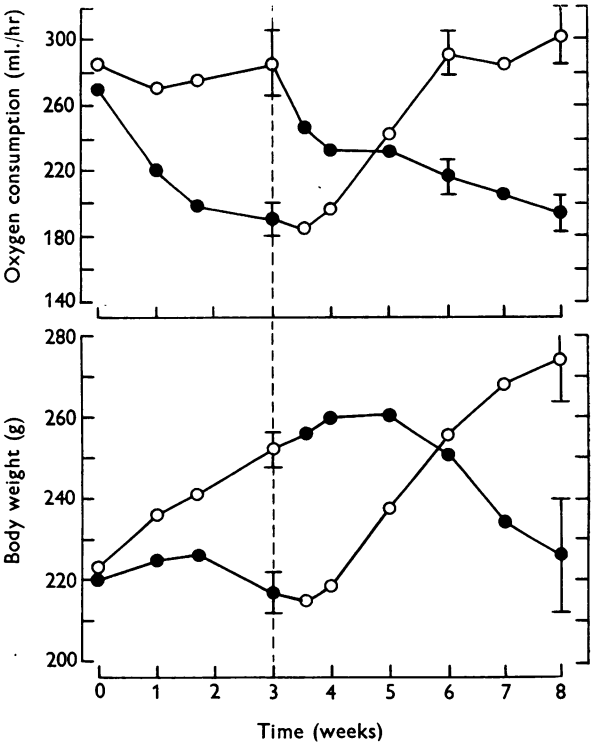

Fig. 1. Oxygen consumption and body weights of rats kept at 28° C and fed on iodine-deficient-PTU diet, ●, and iodine-deficient diet, ○. The diets were exchanged at 3 weeks, as represented by the change of symbols. Each point is the mean from three rats, the vertical bars represent S.E. of the mean.

Long-term feeding. Seven rats varying in weight from 218 to 326 g were fed on iodine-deficient-PTU diet. After the first week the body weights of six rats showed a gradual fall (Fig. 2). After 8 weeks on the diet it did not seem that a steady state would be established and the rats were therefore given daily injections of 20 μg L-thyroxine. Recovery of growth soon followed these injections. The body weight of one rat showed, after the first week, a rapid fall and 4 weeks later it had lost 81 g. This rat was given daily injections of thyroid hormone at the beginning of the fifth week. Recovery in growth rate soon followed.

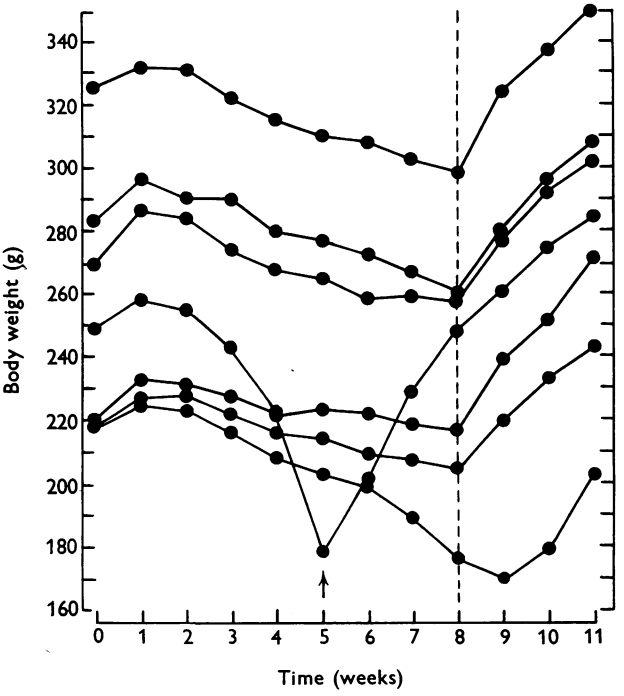

Fig. 2. Body weights of rats kept at 28° C and fed on iodine-deficient-PTU diet. Each point represents the weight of an individual rat. The rat represented by the dot nearest the arrow received daily subcutaneous injections of 20 μg L-thyroxine beginning with the fifth week. The remaining six rats received the same dose beginning with the eighth week.

The effects of the basal diets

There was a high percentage of deaths in the control group on commercial diet (Table 1). This makes it difficult to assess the effects of propylthiouracil (PTU) in the commercial diet. However, PTU does seem to reduce the survival time of rats fed on this diet. Rats fed on the commercial-PTU diet for 4 weeks before cold exposure died in about 17 days when exposed to cold; those fed on the iodine-deficient-PTU diet for the same period before exposure to cold died in less than 1 day.

The results of an experiment in which rats on the commercial-PTU diet received replacement doses of L-thyroxine (T_4) are shown in Table 2. The effects of the doses greater than 2·5 μg/day on survival time cannot be readily compared because of the continued survival of four rats 10 weeks after withdrawal of the hormone injections. The results show, however, that it is possible for rats on the commercial-PTU diet to live for a long

time at 4° C if they are first allowed to become adapted to the cold. Changing the food of the surviving rats to the iodine-deficient-PTU diet resulted in death of all four within 3 weeks.

TABLE 1. Average survival times at 4° C of hypothyroid rats

	At 28° C		At 4° C		
	Initial weight (g)	Final weight (g)	No. of deaths	Weight at death (g)	Survival time (days)
Purina diet					
PTU 0·05 %	223·0 ± 2·8	247·2 ± 4·7	4	216·8 ± 1·0	17·2 ± 0·5
Control	222·2 ± 3·3	266·0 ± 5·1	3	224·3 ± 2·9	25·7 ± 3·4
Iodine-deficient diet					
PTU 0·05 %	226·0 ± 2·9	228·0 ± 6·6	4	217·2 ± 1·2	1·0
Control	223·5 ± 3·7	281·2 ± 7·0	0	—	> 91

All rats were kept at 28° C for 4 weeks before exposure to cold; values given are the mean ± S.E. of the mean; $n = 4$ for each group.

TABLE 2. Average survival times at 4° C of rats fed on a commercial diet containing 0·05 % propylthiouracil and receiving daily subcutaneous injections of L-thyroxine

	Injection period		Post-injection period		
Dose (μg/day)	No. of deaths	Survival time (days)	No. of deaths	Survival time (days)	No. of survivors (at 13 weeks)
1·25	4	18·8 ± 1·2	—	—	0
2·50	2	18·0 ± 3·0	2	13·0 ± 2·0	0
5·00	0	—	2	5·5 ± 1·9	2
10·0	0	—	4	11·8 ± 1·7	0
20·0	0	—	2	7·0 ± 4·0	2

All rats were kept at 28° C for 4 weeks before cold exposure; injections were begun 1 week before exposure and continued for 4 weeks; values given are the mean ± S.E. of mean; $n = 4$ for each group.

The effects of the degree of depletion of thyroid hormone

Survival time in the cold decreased exponentially with length of time of previous feeding on anti-thyroid diet (Table 3). The relationship between the two variables can be described by the linear equation:

$$\log Y = 0{\cdot}864 - 0{\cdot}0293X \ (r = -0{\cdot}989,\ P < 0{\cdot}001),$$

where Y = survival time in days and X = time in days on the anti-thyroid diet before exposure to cold.

The effects of previous cold exposure

Previous exposure to cold increased the survival time of rats fed on iodine-deficient-PTU diet, the survival time being about 1 week with no previous cold exposure and about 3 weeks after 8 or more weeks of exposure (Table 4).

TABLE 3. The effects of the length of time on an iodine-deficient diet containing 0·05% propylthiouracil (PTU) before cold exposure on the survival time of rats at 4° C

Period at 28° C with PTU			Period at 4° C with PTU	
Days on PTU diet	Initial weight (g)	Final weight (g)	Survival time (days)	Weight at death (g)
0		221·0 ± 2·5	7·5 ± 0·4	194·0 ± 3·3
7	222·0 ± 0·7	231·5 ± 3·5	4·0 ± 0·2	217·2 ± 2·2
14	224·5 ± 4·0	236·2 ± 5·3	3·1 ± 0·4	212·2 ± 4·8
21	225·0 ± 3·1	230·2 ± 4·8	2·0 ± 0·3	212·2 ± 4·3
28	226·0 ± 2·9	228·0 ± 6·6	1·0	217·2 ± 1·2

Values given are the mean ± S.E. of mean; $n = 4$ for each group.

TABLE 4. The effects of the length of previous exposure to cold on the survival times at 4° C of rats fed on an iodine-deficient diet containing 0·05% propylthiouracil (PTU).

Period at 4° C without PTU			Period at 4° C with PTU	
Days of exposure	Initial weight (g)	Final weight (g)	Survival time (days)	Weight at death (g)
0		221·0 ± 2·5	7·5 ± 0·4	194·0 ± 3·3
7	221·2 ± 2·4	214·2 ± 5·8	17·5 ± 2·4	187·0 ± 5·6
14	221·2 ± 1·5	212·8 ± 3·8	17·8 ± 0·9	193·5 ± 4·6
35	281·2 ± 6·9	289·2 ± 5·5	17·2 ± 1·1	257·8 ± 4·6
56	219·5 ± 0·9	258·5 ± 8·3	24·8 ± 4·4	230·2 ± 10·2
84	222·0 ± 0·8	259·8 ± 4·3	22·8 ± 1·5	233·8 ± 3·5

Values are the mean ± S.E. of mean; $n = 4$ for each group.

The effects of thyroid hormone replacement

Eighty rats were divided into twenty groups of four rats each and fed on iodine-deficient-PTU diet. The animals were initially kept at 28° C. After 3 weeks they were given either L-thyroxine (T_4) or triiodo-L-thyronine (T_3) injections for 1 week and then transferred into the cold room. The injections of thyroid hormones were continued for a further 4 weeks.

Table 5 shows the survival times of rats that died during the injection period and those that died after withdrawal. The minimal doses of T_3 and T_4 for survival up to 4 weeks are 1·25 μg/day/rat. However, the body weights of the rats receiving T_4 fell continuously, so that it is doubtful if they could have survived much longer on this dose (Fig. 3). The daily doses of T_3 and T_4 that resulted in changes in body weight similar to those of control rats were 1·25 and 5·0 μg/rat, respectively. These doses are considered to be the minimal for survival at 4° C. Increasing the daily doses above these values resulted in increased rates of growth. The optimal daily doses per rat for growth at 4° C were found to be 5·0 and 80 μg for T_3 and T_4, respectively. Further increases in the amounts given resulted in decreased growth rates; these were, however, still higher than those of the control animals.

TABLE 5. Average survival times at 4° C of rats fed on an iodine-deficient diet containing 0·05% propylthiouracil and receiving daily subcutaneous injections of triiodo-L-thyronine (T_3) or L-thyroxine (T_4)

Dose (μg/day)	Injection period: No. of deaths T_3	Injection period: No. of deaths T_4	Injection period: Survival time (days) T_3	Injection period: Survival time (days) T_4	Post-injection period: No. of deaths T_3	Post-injection period: No. of deaths T_4	Post-injection period: Survival time (days) T_3	Post-injection period: Survival time (days) T_4
0·0391	4		1·2 ± 0·2		—		—	
0·0781	4		1·5 ± 0·3		—		—	
0·1562	4		4·0 ± 0·8		—		—	
0·3125	4	4	14·8 ± 3·8	4·5 ± 0·8	—	—	—	—
0·625	3	4	26·0 ± 1·0	9·2 ± 1·2	1	—	5·5	—
1·25	0	0	—	—	4	4	12·5 ± 1·9	10·0 ± 1·6
2·50	0	0	—	—	4	4	17·0 ± 1·9	10·0 ± 3·4
5·00	0	0	—	—	4	4	19·2 ± 2·2	18·5 ± 0·6
10·0	0	0	—	—	4	4	19·2 ± 2·9	17·8 ± 1·1
20·0	0	0	—	—	4	4	17·8 ± 1·7	15·2 ± 5·5
40·0		0		—		4		20·5 ± 2·4
80·0		0		—		4		27·5 ± 1·8
160·0		0		—		4		16·0 ± 6·4

All rats were kept at 28° C for 4 weeks before exposure to cold; injections were begun 1 week before and stopped 4 weeks after cold exposure; values for survival times are means ± S.E. of the means; $n = 4$ for each group.

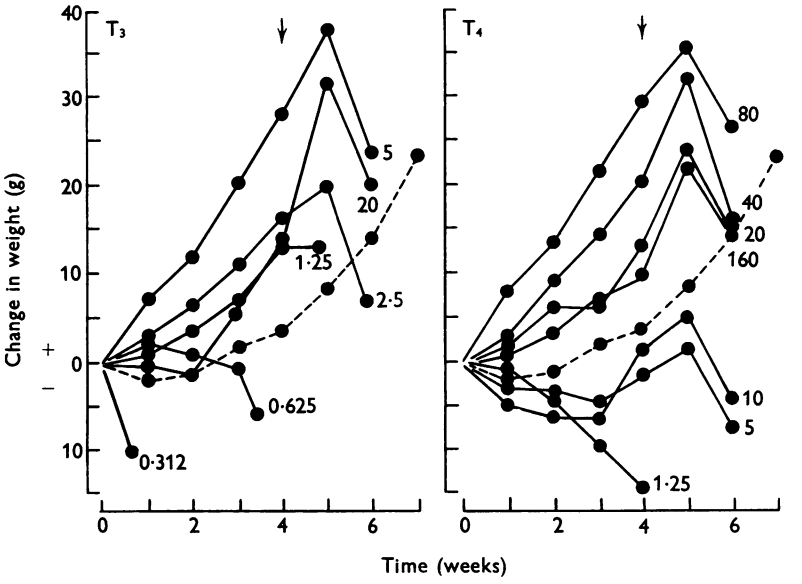

Fig. 3. The effects of triiodo-L-thyronine (T_3) and L-thyroxine (T_4) on the body weights of the rats in Table 5. Each solid line represents the average from a group of four rats and the nearby numbers the dose in μg/day. The interrupted line indicates the average change for a group of eleven control rats fed on the iodine-deficient diet. The arrows indicate the points at which injections were stopped

Rats receiving 20 μg/day of T_3 showed a rapid fall in body weight while in the warm room (Fig. 4); this was converted into a rise after they were transferred to the cold room.

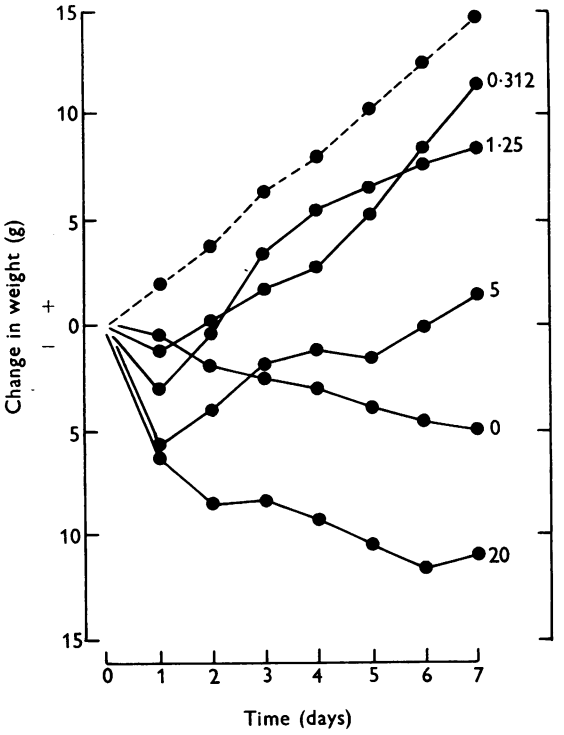

Fig. 4. The effects of triiodo-L-thyronine on the body weights of the rats in Table 5 while kept at 28° C. Each solid line represents the average from a group of four rats and the nearby numbers the dose in μg/day. The interrupted line indicates the average change for a group of eleven control rats.

To determine the minimum requirement of cold-adapted rats for thyroid hormone two groups of rats living at 4° C and fed on iodine-deficient-PTU diet received replacement doses of T_3 of either 5 μg/day or 1·25 μg/day. After 4 weeks of cold-exposure the doses were reduced to 0·625 μg/day for all rats. The dosage for rats that survived 11 weeks of cold exposure was further reduced to 0·312 μg/day. The results are summarized in Fig. 5. Three of the four rats that received 5 μg/day during the initial period of 4 weeks survived for 7 weeks on 0·625 μg/day, but died in about 2 weeks after the dosage was further reduced. Of the four rats that received 1·25 μg/day during the initial period only one survived 7 weeks on 0·625 μg/day. The survival time of cold-adapted rats receiving 0·625 μg/day is related to the initial dose of T_3. This fact complicates interpretation of

the results. However, the majority of the animals receiving 1·25 μg/day did not survive for long on 0·625 μg/day. It seems, therefore, that cold adaptation does not materially reduce the daily requirement for exogenous thyroid hormone.

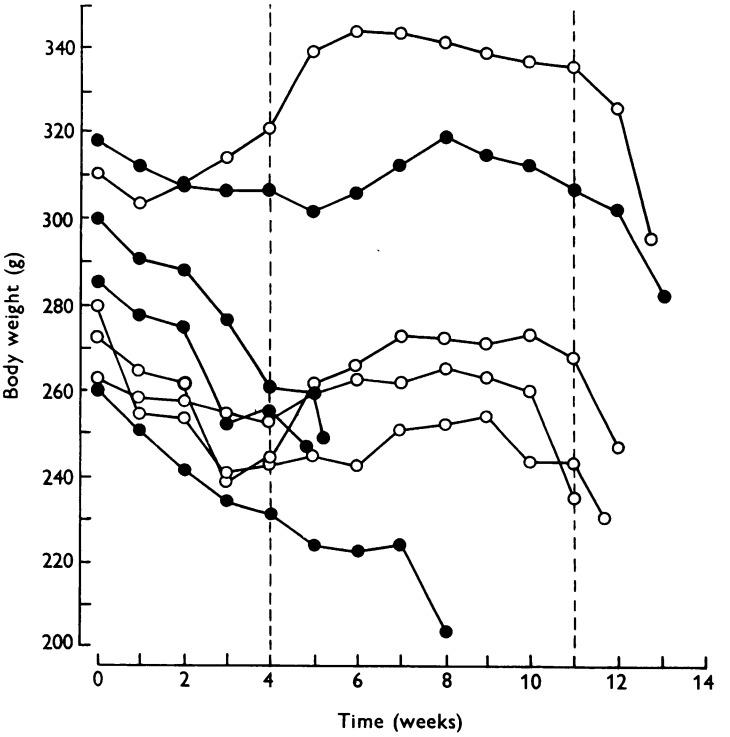

Fig. 5. Body weights and survival times of rats fed on iodine-deficient-PTU diet and kept at 4° C. Each point represents the weight of a single rat. During the first 4 weeks of cold exposure the rats received daily subcutaneous injections of triiodo-L-thyronine, either 5 μg (○) or 1·25 μg (●). From the fourth to the eleventh week all rats received 0·625 μg/day. Rats surviving 11 weeks of cold exposure received 0·312 μg/day.

DISCUSSION

One of the difficulties encountered when comparing the resting metabolic rates of normal and hypothyroid rats is the discrepancy in body weights of the two groups. In the present experiments this difficulty can be obviated by comparing the oxygen consumption of the rats 3 weeks after 'cross-over' (Fig. 1). At this time the average body weights of the two groups are not significantly different while the oxygen consumption of the PTU-fed rats is about 75 % of the group not fed on PTU. This observation and the fact that the body weights of the animals fell during the period on PTU feeding strongly suggest that suppression of thyroid function has

occurred. Since the effects on body weight and oxygen consumption can be reversed either by removal of the PTU (Fig. 1) or by replacement of thyroid hormone (Fig. 2) it can be assumed that the iodine-deficient-PTU diet does not have any deleterious side effects.

The gradual and continuous deterioration of the rats, as indicated by the reduction in their body weights, while being fed on the PTU diet leads one to doubt the validity of the current belief that athyroid animals can survive 'indefinitely' (Leblond & Eartly, 1952) in a warm environment. The amount of exogenous thyroid hormone necessary for survival of rats at 4° C is extremely small (about 1·25 μg/day/rat for T_3). The combination of reduced utilization and reduced requirement for survival at 28° C would result in greatly prolonged survival times. It may well be that they have not been kept under observation long enough. Further experiments will be required to substantiate this.

The high negative correlation between survival time in the cold and length of previous feeding on iodine-deficient-PTU diet (Table 3) is not unexpected and confirms the view that rats cannot survive in the cold without some circulating thyroid hormone. The rats that survived the experiment summarized in Table 2 had been on the commercial-PTU diet for a total of 17 weeks. They were eating, at the end of the experiment, about 30 g of food per day which contained about 15 mg PTU. The fact that they were alive and doing well at that time but died after the diet was changed to iodine-deficient-PTU strongly suggests that the animals were obtaining sufficient hormonally active iodine from the commercial diet. The difference in survival times of rats fed on commercial-PTU and rats fed on iodine-deficient-PTU diets (Table 1) supports this hypothesis. It is therefore necessary to take into consideration the type of diet used when interpreting results of experiments in which thyroid hormone production has been prevented either by thyroidectomy or by the addition of a blocking agent to the diet.

Table 4 confirms previous observations that survival time in the cold of rats fed on an anti-thyroid diet is increased by prior cold adaptation. However, while 1·25 μg/day of T_3 is sufficient to maintain the life of rats with no previous cold exposure (Table 5), rats that have been maintained on this dose for 4 weeks die if the dose is reduced (Fig. 5). Thus adaptation to cold does not lead to a reduction in requirement for thyroid hormone. The increased survival times shown in Table 4 could be due to a number of other factors. One possibility is that it may require a longer time to block the thyroid function of cold-adapted rats. Another possibility is that the combined effects of cold exposure and hypothyroidism may be a greater strain on the animal than that resulting from hypothyroidism after the animal has been allowed to compensate for cold stress.

The finding that increasing the daily dose of thyroid hormone above that required for survival in the cold results in greater than normal growth rates (Fig. 3) suggests that the requirement for optimal growth in the cold may be greater than the amount normally supplied by the gland. The optimal daily dose of T_3 and T_4 for growth of comparable rats living at 28° C are 0·312 and 5·0 μg/rat respectively (Hsieh, unpublished data). Thus the requirement for optimal growth increases sixteenfold at 4° C, while available evidence suggests that thyroid glands of rats exposed to this temperature are only twice as active as at 28° C (Dempsey & Astwood, 1943; Cottle & Carlson, 1956; Woods & Carlson, 1956). It seems, therefore, that there may be a relative insufficiency of thyroid hormone in normal rats exposed to cold. This could account for their retarded growth.

Rats receiving 20 μg/day of T_3 showed a rapid fall in weight while at 28° C (Fig. 4) which was converted into a rise when the animals were transferred to the cold-room. Rats maintained on this dose at 28° C develop hypermetabolism (increase of about 120 %) and fever (about 40° C or 104° F) and die in about 3 weeks. A similar relationship between the toxicity of thyroxine and environmental temperature has been shown by Draize & Tatum (1932). These facts strongly suggest that cold exposure does not increase the sensitivity of rats to thyroid hormone. The protective action of cold exposure against high doses of exogenous thyroid hormone may be due to the combined effects of the following: (1) greater rates of heat loss protecting against hyperthermia; (2) increased food intake causing increased excretion of thyroid hormone in the faeces (Van Middlesworth, 1957); (3) increased cardiac output leading to greater rates of clearance via the liver and kidneys; and (4) increased utilization of thyroid hormone by the tissues. It is possible that the last three factors may also be the cause of the increased requirement for thyroid hormone in cold-exposed animals.

The results of the present experiments give no support to the contention that the thyroid gland actively stimulates, via its hormone secretion, the metabolism of cold-exposed animals. Since increases in the plasma protein-bound-iodine (PBI) concentrations have never been demonstrated, the hypothesis can only be based on the following arguments: (1) the increases in plasma PBI that occur are undetectable by existing methods; (2) cold exposure may lead to a change in the quality of the hormone secreted; (3) an increase in the sensitivity of the tissues to thyroid hormone may occur. The usual analytical methods can detect 0·5 μg PBI/100 ml. plasma, that is about 15 % of the normal level in rats (Jones & Van Middlesworth, 1960). In at least one report a significant reduction in serum PBI has been shown (Ershoff & Colub, 1951). It is therefore reasonable to assume that if an increase in PBI concentration did occur it would

have been detected. A shift from thyroxine secretion to triiodothyronine secretion could result in stimulation of metabolism without any apparent change in plasma PBI concentration. Rats given seven daily injections of T_3 10 μg/100 g body weight increase their oxygen consumption by about 70 % (Stasilli, Kroc & Meltzer, 1959). We have found that the effects of T_3 are cumulative and that after 3 weeks on this dose the surviving rats increase their oxygen consumption by 120 %. While this increase is of the same order of magnitude as that found in cold-exposed rats (Hsieh & Carlson, 1957) the dose of T_3 required to produce this response is definitely toxic. The daily rate of secretion of thyroid hormone by rats living at 25° C has been estimated to be equivalent to about 3–5 μg L-thyroxine (Woods & Carlson, 1956). Even if this amount were secreted entirely as T_3 it would be insufficient to cause a doubling of the oxygen consumption of rats without a concomitant increase in the sensitivity of the tissues to thyroid hormone. The present experiments, however, clearly show that cold exposure does not result in increased sensitivity to thyroid hormone. On the contrary, cold exposure has a definite protective action against lethal doses of T_3.

Measures which stimulate heat production, such as administration of 2,4-dinitrophenol (Wolff, Rubin & Chaikoff, 1950) or pyrogenic bacterial extracts (Goldberg, 1954) reduce plasma PBI concentrations. This has been shown to be due in part to increased excretion or utilization of thyroid hormone (Goldberg, Wolff & Greep, 1955). The calorigenic responses of animals to dinitro-ortho-cresol (Barker, 1946) and to adrenaline (Swanson, 1956) are roughly proportional to the amount of circulating thyroid hormone. Thus thyroid hormone may be essential for support of cell activity, as suggested by Rand *et al.* (1952), and increased cellular activity may lead to increased utilization of thyroid hormone. The role of the thyroid gland is thus simply one of responding to increased need for its hormone.

SUMMARY

1. The effects of the basal diet, previous exposure to cold, degree of thyroid hormone depletion and the amount of thyroid hormone replacement on the survival time of male albino rats living at 4° C and fed on diets containing 0·05 % propylthiouracil (PTU) have been investigated.

2. Rats fed on a commercial diet and PTU for 4 weeks before cold exposure died in about 17 days, while those fed on an iodine-deficient diet and PTU for the same period before exposure died in less than 1 day.

3. The daily doses of triiodo-L-thyronine (T_3) and L-thyroxine (T_4) that resulted in growth rates similar to controls were 1·25 and 5·0 μg/rat, respectively. Rats maintained on 1·25 μg/day T_3 for 4 weeks in the cold

died when the dose levels were reduced. Thus cold adaptation does not reduce the requirement for thyroid hormone.

4. The optimal daily doses of T_3 and T_4 for growth were 5·0 and 80 μg/rat respectively. The retarded growth of normal rats living in the cold may be due to a relative insufficiency of thyroid hormone.

5. Rats living in the cold can tolerate doses of T_3 which are toxic to those living at 28° C. Thus cold exposure does not result in increased sensitivity to thyroid hormone.

6. The results, taken with the findings of others that plasma protein-bound-iodine concentrations of cold-exposed animals are not elevated, do not support the contention that the thyroid gland stimulates, via its hormone secretion, the metabolic rate of cold-exposed animals.

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