PART VI

STUDIES ON THE ROLE OF THE THYROID GLAND

"If the pituitary is viewed as 'the leader of the endocrine orchestra', perhaps the thyroid may be regarded as the first violin"

— Salter, W.T.
PART VI

SECTION I

HISTOLOGICAL STUDY OF THE THYROID GLAND

"No longer can the experimental pathologist hope to gauge thyroid function with a microscope".

— Salter, W. T.
Introduction and review

Magnus Levy (quoted by Spence, 1953) first showed in man that heat production was decreased in spontaneous and experimental myxœdema and was increased by thyroid feeding. This has been confirmed repeatedly, which has led to the unanimously accepted view that one of the most fundamental biological actions of the thyroid is the regulation of metabolic activity. A mg. of thyroxine given to a man can raise the heat production by 1008 calories (Boothby and Sandiford, 1924).

Thyroxine is the principal circulating thyroid hormone. Triiodothyronine, which is more active, occurs in relatively small amounts (Pitt-Rivers, 1958). Their mode of action is not yet clarified. The prevalent view links the action with uncoupling of the respiratory chain phosphorylation (Holzer, 1959).

Many factors modify the activity of the thyroid, such as activities of the other endocrine glands, environmental temperature, nutrition and general health. Its activity is to a great extent regulated by the thyroid stimulating hormone (TSH) of the anterior pituitary, while the thyroid itself exerts a restraining effect on the secretion of TSH by a negative feedback action on the pituitary (Salter, 1950; von Euler and Holmgren, 1956; Salaman, 1964). Recent studies
(Brown-Grant, 1960; Solomon and Dowling, 1960; D'Angelo and Synder, 1963; Guillemin et al. 1963), have led to the concept of hypothalamo-hypophyseal-thyroid axis: the hypothalamus controls the thyroid activity by regulating the secretion of the pituitary.

The thyroid is markedly influenced by changes in the external thermal environment. Increased activity in cold and decreased activity in heat have been well documented.

This environmentally impressed alterations in the activity point to the important role of the thyroid gland in calorigenesis in a cold environment. Dempsey and Astwood (1943), found the release of thyroid hormone increased in rats exposed to cold. In rats exposed to 0°-2°C (Leblond et al. 1944), the rate of fixation and turn over of radio-iodine was definitely increased by 7 days and became maximum after 26 days (2.5 times the normal), but after 40 days of exposure returned to the normal level. Increased secretion of thyroxine in cold has also been reported by others (Rand et al. 1952; Brown-Grant et al. 1954a; Brown Grant, 1956a, 1956b; Woods and Carlson, 1956; Harland and Goldberg, 1964; Tamada et al. 1965).

Other evidences of increased thyroid activity in cold are (i) increased oxygen consumption of animals of various species (Benedict and MacLeod, 1929; Ring, 1936, 1938, 1939, 1940), (ii) inability of the thyroidectomised animals to survive
refrigeration for more than a few days (Korenchevsky, 1926; Ring, 1939; Leblond and Gross, 1943), (iii) histological evidence of increased activity (Cramer, 1916; Mills, 1918; Cramer and Ludford, 1926; Kenyon, 1933; Baillif, 1937; Starr and Roskelly, 1940; Bernstein, 1941; Ariel and Warren, 1943; Lesser et al., 1949; DelConte and Stux, 1954; Dempsey and Peterson, 1955; Stevens et al., 1955) and (iv) increased thyroxine requirement in cold as evidenced by the greater replacement dose of thyroxine required to maintain the metabolic rate in rats thyroidectomised surgically (Woods and Carlson, loc. cit.), or "medically" (Rand et al., loc. cit.). Increased thyroxine requirement may not mean increased utilisation.

While the laboratory rat at 6°C required 5.5 mcg./100 gm. body weight to replace the endogenous production, the winter outdoor rats required only 1.8 mcg. (Héroux, 1963). The rapid loss of thyroxine observed in the cold acclimated animals (Mann et al., 1951; Intoccia and Van Middlesworth, 1959), may be the cause of the increased requirement (Héroux, loc. cit.).

The level of serum protein bound iodine (PBI) has been found to be very little affected. Unchanged or even slightly lower level of PBI has been reported in sheep (Freinkel and Lewis, 1957), in rats (Rand et al., loc. cit.; Gregerman and Crowder, 1963), in guinea-pigs (Stevens et al., loc. cit.) and in man (Ingbar and Bass, 1957). Gottschalk and Riggs (1952), however, reported increased serum PBI in man under prolonged cold exposure.
Some studies showed that thyroidectomised rats (Leblond and Gross, loc.cit.; Ring, 1936; Lee and Lee, 1937), and the rats treated with antithyroid drugs (Macbeth and Noble, 1949) were capable of well marked metabolic response to cold although they were unable to sustain this high metabolic rate for more than a few days, meaning thereby, that the thyroid was not essential for the metabolic response during acute exposure to cold.

The thyroid response to cold depends upon the intensity of cold. Acute exposure to progressively more severe cold may lead to increased, unchanged or decreased activity (Brown-Grant and Pethes, 1960). At a body temperature of 15°C-20°C, the thyroid of rat has been found completely inactive (Verzar et al. 1953). This inhibition of activity is a nonspecific reaction to the stress component of the intense cold stimulus, a phenomenon that has been reported with a multitude of stressors. (Williams et al. 1949; Hamolsky et al. 1951; Wase and Repplinger, 1953; Badrick et al. 1954; Brown-Grant et al. 1954a, 1954b; Brown-Grant, 1956a, 1956b; Gernig et al. 1958). Inhibition of thyroid activity has been observed usually at a temperature less than 5°C (Brown-Grant, 1954b). However, increased thyroid activity under similar conditions has also been found by some e.g. in guinea-pig and rhesus monkey with bacterial toxins (Gernig et al. loc.cit.), in surgical stress (Perry
and Gemmell, 1949), in febrile patients (Beck et al., quoted by Gernig et al. loc.cit.) and following stress of X' irradiation (Botkin et al. 1952).

The increased activity of the thyroid in cold is brought about by the increased release of the pituitary TSH, but the mechanism of action of cold to bring out this release of TSH is not yet solved satisfactorily. Just how the thyroid hormone acts at cellular level in the cold exposed animals is also not clear. It provides more heat, possibly by uncoupling oxidative phosphorylation which produces more heat but less ATP (Hoch, 1962).

Comparatively little work has been done on the thyroid activity in a hot environment. A hypoactive thyroid has been a constant finding as is expected on the basis of its calorigenic action. Such studies have shown decreased release of thyroid hormone (Dempsey and Astwood, loc.cit.; Brown-Grant et al. 1954a) and decreased rate of fixation and fractional turn over rate of radioiodine (Leblond et al. loc.cit.). Five weeks of exposure of mice to 91°F reduced the rate of I^{131} uptake to half of the control value (Hellmann and Collins, 1957). In summer the rate of thyroid secretion was found to decline in mice (Hurst and Turner, 1947). Low requirement of thyroxine in a hot environment can be inferred from the observation of more toxicity of thyroxine to guinea-pigs kept at 32°C than to
those at 20°C (Schmidt and Schmidt, 1938). Hot exposure has also been shown to decrease the output of TSH (Goldberg et al. 1955). Histological studies have also shown hypoactivity of the thyroid in the heat-exposed animals of various species (Mills, loc.cit.; Cramer and Ludford, loc.cit.; Kenyon, loc.cit.; Bailiff, loc.cit.; Schmidt and Schmidt, 1938b; Bernstein loc.cit.; Hellmann and Collins, loc.cit.).

Experimental

The specimens of the thyroid glands were collected from the same rats which were used for the study of A-V sugar difference. The thyroid was removed after the collection of blood. There were 16 rats in each group of the "control", "hot" and "cold". The gland was processed and stained according to standard methods (Lillie, 1965). Bouin's fluid was used as a fixative. Haematoxylin-eosin and Mallory's PTAH stain were used. In addition to usual histological study, the ratio of the vesicular to the pyknotic nuclei in the follicles was also determined. The latter has been termed "nuclear index". In each lobe 20 central follicles were studied for this purpose and the mean taken.

Results

"Control" (Fig. 19)

The thyroid follicles were of variable sizes, even in the central portions. They were lined by a single layer of cuboidal cells except a few which showed flattened cells.
The follicles were filled with well-stained colloid. Three rats showed pale colloid. No vacuole was seen in the colloid. The blood vessels were not very conspicuous.

In the "hot" animals (Fig. 20) only difference noted was the occurrence of lightly stained colloid in a few follicles of 4 rats. 7 "cold" rats showed lightly stained colloid in a number of follicles and in one only marginal vacuoles were observed (Fig. 21).

Significant difference was noted in the "nuclear index". The figures for the "control", "hot" and "cold" rats were 5.09, 3.49 and 12.15 respectively.

Discussion

Previous histological studies have shown that, in general, it takes several days of thermal exposure to produce demonstrable changes in the vascularity, cell height, and colloid character and other features. However, a few observers could detect changes within half an hour to 2 hours of application of this stimulus (table 18).

Studies of radioiodine metabolism have revealed that injection of TSH could elicit thyroid response in 1-2 hours in rabbits (Brown-Grant et al. 1954a), in 2-3 hours in rats (Wolff, 1951), emotional stress in less than 3 hours and cold stimuli (2°C-21°C) in less than 4 hours in rabbits (Brown-Grant et al. 1954a). Almost immediate inhibition of thyroid activity was noted in rats subjected to torniquet shock by Hamolsky et al. (loc. cit.).
Table 18

Minimum period of thermal exposure as reported by various workers to produce demonstrable histological changes of the thyroid

<table>
<thead>
<tr>
<th>Author</th>
<th>Animal</th>
<th>Temperature range</th>
<th>Period of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills (1918)</td>
<td>Rabbit and guinea-pig</td>
<td>-5°C to 10°C</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>Rabbit, guinea-pig and cat</td>
<td>27°C to 37°C</td>
<td>3 days</td>
</tr>
<tr>
<td>Cramer and Ludford</td>
<td>Mouse</td>
<td>Several days in open cold room and then to 37°C</td>
<td>6 hours</td>
</tr>
<tr>
<td>(1926)</td>
<td></td>
<td>Several days at 37°C and then in open cold room</td>
<td>4 hours</td>
</tr>
<tr>
<td>Kenyon (1933) Rat</td>
<td>-4°C to 2°C</td>
<td></td>
<td>No change up to 24 hours. Change after 10 days.</td>
</tr>
<tr>
<td>Baillif (1937) Rat</td>
<td>-4°C, 34°C, 36°C and 38°C</td>
<td></td>
<td>Few hours</td>
</tr>
<tr>
<td>Starr and Roskelly</td>
<td>Rat</td>
<td>12°C to 17°C</td>
<td>3 days</td>
</tr>
<tr>
<td>(1940)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernstein (1941) Rat</td>
<td>23°F</td>
<td>107.6°F for 10 minutes each day</td>
<td>2 days</td>
</tr>
<tr>
<td>Ariel and Warren</td>
<td>Rabbit</td>
<td>10°C-27°C</td>
<td>1/2 to 2 hours</td>
</tr>
<tr>
<td>(1943)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pichotka (1952,1953)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DelConte and Stux (1954) Guinea-pig</td>
<td>At least 10°C less than that of the surrounding</td>
<td>1/2 hour</td>
<td></td>
</tr>
<tr>
<td>Stevens et al. (1955)</td>
<td>Guinea-pig</td>
<td>7°C+2°C</td>
<td>7 days</td>
</tr>
</tbody>
</table>

*Cited by Söderberg (1959)
≠ Cited by Bigelow and Sidlofsky (1961)
Electric shock could produce increase of serum PBI in less than 5 minutes (Németh, quoted by Söderberg, 1959).

Some clinical studies such as the appearance of "thyroid storm" in thyrotoxic patients after various stresses (McArthur et al. 1947; Rives and Shepard, 1951) also showed that the thyroid could respond very rapidly.

The salient histological features observed in the exposed animals are the increased occurrence of follicles containing pale colloid and changes in the 'nuclear index'. The former is regarded as a sign of follicular activity (Cremer, loc. cit.; Baillif, loc. cit.). As only 4 out of the 16 heat-exposed animals showed this change (cf. "control"-3) no importance can be attached to this feature in the "hot" animals. The same change observed in 7 'cold' rats perhaps points to enhanced thyroid activity in cold.

Changes in the 'nuclear index' appear to be significant. During the histological study a striking feature noted was the frequent occurrence of pyknotic nuclei in the follicles of the "control" and "hot" animals. This led to the study of the ratio of the vesicular to pyknotic nuclei in the follicles. This ratio has been designated as "nuclear index".

In the thyroid follicles two types of cells can be distinguished—chief and colloid cells which actually
represent the active and relatively inactive stage respectively of the same cell (Baillif, loc.cit.). The former shows vesicular lightly stained nucleus while the latter, a densely stained nucleus with tendency to pyknosis. Cramer and Ludford (loc.cit.) also noted the loss of the staining power of the nuclei during intense thyroid activity. Considering in this light a higher 'nuclear index' found in the "cold" animal indicates increased thyroid activity and the reverse holds true for the "hot" animals. This is in accord with the prevailing concept of thyroid activity in hot and cold environments.

Summary

Rats controlled at 30°C when exposed to 6°C±1°C for 2 hours showed evidence of increased thyroid activity while after exposures to 41°C ± 0.5°C for the same duration the thyroid was possibly hypoactive. A new histological method ('nuclear index') has been described to detect rapid change in thyroid activity.

References


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__________ Am. J. Physiol., 125 : 244, 1939.

__________ Am. J. Physiol., 131 : 357, 1940.


PART VI
SECTION II

STUDIES ON THE THERMOGLYCEMIC RESPONSE AND
GLUCOSE TOLERANCE TEST IN HYPOTHYROID ANIMALS.
Introduction and review

Both experimental and clinical evidences suggest that the thyroid influences carbohydrate metabolism. However, proper evaluation of its role is difficult as its direct effects are intricately mixed up with those exerted through insulin and epinephrine.

The thyroid hormone specifically increases the intestinal absorption of glucose and galactose (Althausen and Stockholm, 1938). In hyperthyroid state the oral glucose tolerance test shows a high peak because of rapid absorption of glucose, but the return to the normal level is earlier than in cases of diabetes (Althausen et al., 1940) and the tolerance improves after thyroidectomy (John, 1942). The intravenous glucose tolerance test is not altered (Houssay, 1946). In hypothyroidism the curve is flat due to the diminished rate of absorption of glucose and the abnormality disappears if glucose is given intravenously (Soskin and Levine, 1952).

The administration of thyroid hormone decreases the glycogen content in various species of animals. Liver glycogen disappears even when the animals are on carbohydrate rich diets (Cramer and Krause, 1913). Heart muscle glycogen is also reduced (Lawrence and McCance, 1931), while the skeletal muscle glycogen is affected last (Houssay, loc.cit.). Glycogen synthesis has been found to be decreased
in the liver and the muscle in hyperthyroidism and this is linked with low ATP content (Hoch, 1962).

The thyroid hormone increases the utilisation of glucose by the tissues (Sanger and Huc, 1933; Mirsky and Broh-Kahn, 1936; Burton et al. 1958). According to Marine (1935) the depletion of liver glycogen is due to increased utilisation rather than to any abnormality in hepatic function. Wertheimer and coworkers (Wertheimer and Bentor, 1953; Wertheimer et al. 1954) observed that the cold-induced increase in the utilisation of glucose and glycogen synthesis by the rat diaphragm was abolished by thyroidectomy. Cramer and M'Call (1918) could not detect any impairment of carbohydrate oxidation in thyroidectomised rats. Minjer (1952) from his studies on patients who died of hypothermia in World-war II in Holand and from experimental studies in guinea-pigs concluded that the oxidation of liver glycogen was not or only unsatisfactorily, stimulated in absence of a properly functioning thyroid.

Thyroxine potentiates insulin action. The administration of thyroxine leads to increase in size and number of pancreatic islets and subsequently to disintegration and atrophy (Farrant, 1913; Herring, 1917; Houssay, loc.cit.). Insulin sensitivity is increased in thyrotoxicosis and decreased in hypothyroidism (Houssay, loc.cit.; Elrick et al. 1961).
In human diabetes the thyroid shows a 50% increase in size (Wrenshall et al. 1952). In thyroxine treated rats, the adipose tissue doubles its rate of glucose uptake and CO₂ production at the optimal in vitro dose of insulin (Hagen, 1960).

Whether the thyroid potentiates or antagonises the hyperglycemic action of epinephrine is still undecided (Hoch, loc. cit.), though the potentiation of the calorigenic action of epinephrine by thyroxine is well established (Ring, 1942). Swaonson (1956) has suggested that adrenaline may provide glucose, the utilisation of which is increased by thyroxine; adrenaline action may also be prolonged by the inhibitory action of thyroxine on amine oxidase. According to Spence (1953) there is no convincing evidence that the thyroid hormone increases the secretion of adrenaline.

Increased activity of hexokinase of the leg muscle (Smith and Williams, 1949) and succinoxidase of the liver (Tipton et al. 1946; Smith and Williams, loc. cit.; Tipton, 1950) has been found in rats given thyroxine or thyroid substance. Liver LDH was diminished in such animals (Vestling and Knoepfelmacher, 1950). Both the two principal routes of hexose oxidation in rats, viz. glycolytic and phosphogluconate paths have been reported to be stimulated by the administration of tri-iodothyronine (Spiro and Ball, 1958).
According to Smith (1963), the thyroid hormone is a stimulator of the TPN-dependent dehydrogenases of glucose-6-phosphate and 6-phosphogluconate whereby hexose is shunted into the pentose phosphate pathway with simultaneous reduction of TPN to TPNH. Thyroxine stimulates the following reactions (Smith, loc. cit.).

(i) Glycerophosphate $\rightarrow$ dihydroxyacetone phosphate

(ii) Glucose-6-phosphate $\rightarrow$ 6-phosphogluconate $\rightarrow$ ribose-5-phosphate

(iii) Glucose-6-phosphate $\rightarrow$ glucose.

In view of the above knowledge of the thyroid physiology, the following studies were undertaken in the animals exposed to different ambient temperatures to find out whether the thyroid plays any significant role in carbohydrate metabolism under such thermal environments.

1. Thermoglycemic response in hypothyroid animals.

2. Glucose tolerance test in hypothyroid animals.

Experimental

The experimental procedures were same as described earlier for the normal animals. For the study of thermoglycemic response, 48 rats (wt. 180-200 g.) divided into 2 groups of 24, and 28 rabbits (wt. 1600-1800 g.) divided into two groups of 14 were used. For the glucose tolerance test, 36 rats (wt. 180-200 g.) and 36 rabbits (wt. 1600-1800 g.) each species divided into 3 groups of 12 were utilised.
For inducing hypothyroid state, the antithyroid drug carbimazole (2-ethoxycarbonyl thio-1-methylglyoxaline; Indian Schering Ltd.) was used. This is one of the recent antithyroid drugs, commonly used for the treatment of hyperthyroidism. It is promptly absorbed from the gastrointestinal tract. It is about 10 times as potent as methyl or propyl thiouracil (Dunlop, 1958). It produces hypothyroidism by preventing (a) the conversion of iodide into iodine, (b) the iodination of monoiodotyrosine to form diiodotyrosine (DIT) and (c) coupling of DIT molecules to form thyroxine (Keele and Neil, 1965).

The dose of carbimazole had been chosen following the precedences and trials.

Chaikoff and his associates (Franklin et al. 1944a,b; Schochner et al. 1944) found that on a dose of 4 mg./day of thiouracil for one week, the ability of the rat's thyroid to accumulate radioiodine and to convert the iodide into diiodotyrosine and thyroxine was reduced to one third of the control value. Sadhu and Brody (1947) found 40% reduction of BMR of rats following thiouracil feeding for 17 days in a dose of 15-20 mg./day. In young rats (Salter, 1950) given thiouracil in a concentration of 0.1% in the diet, the thyroid hormone reserve was found exhausted in 5 days. Consideration had also to be given to the
reported atrophy of the adrenal cortex after prolonged thiouracil feeding (Bauman and Marine, 1945; Deane and Greep, 1947; Zarrow and Money, 1949) while choosing the duration of the treatment. In this work, the dose was 5 mg. and 10 mg. per day for the rats and the rabbits respectively. The drug was given in two divided doses at 1000 hrs. and 1600 hrs. respectively in powdered form and mixed with a little milk and bread. The duration of treatment was 4 weeks.

Pre- and post-treatment cholesterol levels of plasma were estimated in 24 animals, to serve as a rough index of hypothyroid state (Salter, loc.cit.). Histological studies of the thyroid of 6 animals, selected at random from each species, were also undertaken.

The mean room temperature during the studies on the thermoglycemic response and glucose tolerance test of rats was 29°C; in case of rabbits it was 30°C.

Results

The cholesterol level (table 19) increased approximately by 39.5% and 29.1% in rats and rabbits respectively. The histological studies (Figs. 22 and 23) showed increased vascularity, hypertrophy and hyperplasia of the follicular cells with formation of new follicles. The follicles had hardly any colloid. In rat the papillae formation was also evident.
Table 19
Blood sugar and cholesterol and rectal temperature of rats and rabbits subjected to heat or cold

<table>
<thead>
<tr>
<th></th>
<th>&quot;Hot&quot;</th>
<th></th>
<th>&quot;Cold&quot;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-exposure</td>
<td>Post-exposure</td>
<td>Pre-exposure</td>
<td>Post-exposure</td>
</tr>
<tr>
<td>RAT Sugar (mg./100 ml.)</td>
<td>79.8±</td>
<td>75.3±</td>
<td>79.1±</td>
<td>64.4±</td>
</tr>
<tr>
<td>Pre-exposure</td>
<td>11.9</td>
<td>13.5</td>
<td>13.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Rectal temp. (°C)</td>
<td>37.6</td>
<td>40.2</td>
<td>37.6</td>
<td>36.4</td>
</tr>
<tr>
<td>RABBIT Sugar (mg./100 ml.)</td>
<td>89.9±</td>
<td>81.5±</td>
<td>88.8±</td>
<td>77.8±</td>
</tr>
<tr>
<td>Pre-exposure</td>
<td>10.8</td>
<td>9.4</td>
<td>13.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Rectal temp. (°C)</td>
<td>39.9</td>
<td>41.6</td>
<td>39.8</td>
<td>38.7</td>
</tr>
</tbody>
</table>

* Mean ± S.D.

't' test: Blood sugar

Rat: "Hot": \( \overline{d} = 4.5; \ SE (\overline{d}) = 1.32 \) Highly significant lowering of blood sugar.

\[ t^\prime = 3.46 \]

"Cold": \( \overline{d} = 14.7; \ SE (\overline{d}) = 2.71 \) -do- -do-

\[ t^\prime = 5.48 \]

Table value of 't' at 1% level = 2.82

Rabbit: "Hot": \( \overline{d} = 8.4; \ SE (\overline{d}) = 3.25 \) Significant lowering of blood sugar.

\[ t^\prime = 2.59 \]

"Cold": \( \overline{d} = 11.0; \ SE (\overline{d}) = 3.53 \) Highly significant lowering of blood sugar.

\[ t^\prime = 3.14 \]

Table value: 5% level = 2.18

1% level = 3.11
Both rats and rabbits showed significant hypoglycemia (table 19) after hot and cold exposures. Four rats and 2 rabbits from each group showed hyperglycemia.

The rats showed a mean rise of rectal temperature of 2.6°C and a mean fall of 1.2°C after hot and cold exposures respectively (table 19). The corresponding figures in the rabbits were 1.7°C and 1.1°C respectively.

The results of glucose tolerance tests have been shown in tables 20 and 21 and figures 24 and 25.

The "hot" rats (table 20, Fig. 24) differed from the "control" rats in that after an initial fall to little above the fasting level the blood sugar rose again and remained at a high level till the end of second hour. On removal to room temperature, blood sugar fell progressively. The curve of the "cold" animals did not materially differ from that of the "control" ones.

In the rabbit (table 21, Fig. 25) the "hot" group showed slightly slower removal of glucose initially. In the "cold" animal the rate of glucose removal was slower throughout the exposure period. The figures 26 and 27 represent comparison of the glucose tolerance of untreated (vide Part IV, Section I) and treated animals.
### Table 20

**Glucose tolerance test of hypothyroid rats**

<table>
<thead>
<tr>
<th>Ambient Temp. °C</th>
<th>Fasting</th>
<th>30 min.</th>
<th>60 min.</th>
<th>120 min.</th>
<th>180 min.</th>
<th>240 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>*86</td>
<td>99</td>
<td>97</td>
<td>80</td>
<td>77</td>
<td><strong>77.0</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>(77.2)</em></td>
</tr>
<tr>
<td>41</td>
<td>95</td>
<td>115</td>
<td>101</td>
<td>103</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>100</td>
<td>91</td>
<td>82</td>
<td>78</td>
<td><strong>77</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>(77.2)</em></td>
</tr>
</tbody>
</table>

*Mean blood sugar in mg./100 ml.

**All figures have been "rounded" and plotted. The actual figure is given within bracket to indicate the rising trend.*

### Table 21

**Glucose tolerance test of hypothyroid rabbits**

<table>
<thead>
<tr>
<th>Ambient Temp. °C</th>
<th>Fasting</th>
<th>30 min.</th>
<th>60 min.</th>
<th>120 min.</th>
<th>180 min.</th>
<th>240 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>*91</td>
<td>300</td>
<td>180</td>
<td>100</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>41</td>
<td>96</td>
<td>315</td>
<td>207</td>
<td>102</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>91</td>
<td>315</td>
<td>224</td>
<td>136</td>
<td>104</td>
<td>98</td>
</tr>
</tbody>
</table>

*Mean blood sugar in mg./100 ml.

**All figures have been "rounded" and plotted. The actual figure is given within bracket to indicate the rising trend.*
Discussion

The animals were rendered undeniably hypothyroid as shown by the rise of blood cholesterol and the histological study. But as neither the cholesterol level nor the histological picture can quantitate the functional status of the thyroid, the degree of hypothyroidism cannot be ascertained. Considering the dose and duration of the treatment with a highly potent antithyroid drug, along with the rise of cholesterol and histological changes, the animals may be regarded as markedly hypothyroid.

In both the species, the thermoglycemic response is in no way different from their untreated fellow animals. It appears that the thyroid is not involved significantly in this response.

The hypothyroid state has not made any difference in the utilisation of glucose by the rats at room temperature and in a hot environment as compared to the untreated ones (Fig. 26). That there has not been any difference at the room temperature is in accord with the prevailing concept that while oral glucose tolerance in hypothyroidism is abnormal due to decreased intestinal absorption, the intravenous glucose tolerance test is normal (Soskin and Levine, loc. cit.). The intraperitoneal absorption is very rapid and there is no evidence to show that peritoneal absorption is impaired in hypothyroidism. The "hot" animals have shown impaired tolerance. As it is seen also in the untreated
ones, this feature is not one of hypothyroid state but is a result of the hot environment. In the cold environment, the blood sugar of hypothyroid animals rose higher compared to the untreated ones, and remained at a level higher than that of the latter. Compared amongst themselves and with corresponding untreated ones (Fig. 27) the treated "cold" rabbits also show impaired glucose utilisation. Others do not show any significant difference.

It can be inferred from the above discussion that the clearance of a glucose load by hypothyroid animals in a cold environment is impaired. This indicates that increased thyroid activity in cold helps in utilisation of glucose. This agrees with the finding of Wertheimer and coworkers (loc. cit.).

Summary

Rats and rabbits made hypothyroid with carbimazole did not show any significant difference in thermoglycemic response and glucose tolerance test at room temperature and in hot environment as compared to the untreated animals. In cold, both rats and rabbits showed impairment of glucose tolerance which has been attributed specifically to hypothyroidism.


Wertheimer, E. and Bentor, V., Metabolism, 2: 536, 1953.