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Responses of Thyroid Activity to Feed Restriction in the Goat

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Abstract

A study of the effect of restriction of feed intake on the deiodination, faecal excretion, distribution and secretion of thyroid hormones was carried out in a group of eight young male goats.

In the control goats fed *ad libitum* no changes in the concentration of circulating thyroxine were observed with increasing age or body weight during the experimental period; however, an increase in thyroxine secretion rate per animal was apparent with increasing age or body weight of the goats.

In feed-restricted goats, no changes in the peripheral deiodination of [^{125}I]thyroxine were observed, though significantly reduced faecal excretion of [^{125}I]thyroxine was seen in goats restricted to 50 or 20% of their *ad libitum* feed intake. Both thyroxine turnover rate and thyroxine distribution volume were reduced by feed restriction. The secretion rate of thyroxine was reduced to 45% of the rate in *ad libitum* fed animals when feed intake was restricted to 20%. Calculation of thyroxine secretion rate per kilogram$^{0\cdot75}$ body weight showed a highly significant correlation with feed intake.

It was concluded that the marked reduction in thyroid activity occurring when feed restriction was imposed would be expected to cause a physiologically significant reduction in metabolic activity.

Introduction

Studies on the effects of feed restriction, malnutrition or starvation on thyroid function in mammals have lead to the general conclusion of a depression in secretion (see Milner 1972). Measurements of thyroid secretion rate in rats and cattle with restriction of feed showed significant decreases (Grossie and Turner 1962; Post 1965). The cause of this decrease is not clearly established, since measurements of circulating TSH in rats and humans on inadequate diets which depress thyroid secretion do not necessarily show reduced TSH concentrations (Srebnik *et al.* 1963; Florsheim *et al.* 1970; Chopra and Smith 1975).

The peripheral utilization of thyroid hormones changes during starvation, with a decrease in the rate of disappearance of thyroxine from the circulation (Nathanielsz 1970). Changes in the pathway of thyroxine metabolism, away from 3,5,3′-triiodothyronine and towards increasing formation of 3,3′,5′-triiodothyronine (a relatively inactive metabolite) have been observed in humans on inadequate caloric intakes (Vagenakis *et al.* 1975).

Changes in the excretion of thyroxine through the faeces have been reported to be related to faecal mass (Van Middlesworth 1957; Reichlin and Koussa 1958), and therefore to feed intake. The excretion of conjugated thyroxine via the bile into the gut contents provides a significant excretory route for the hormone, since little, if any, reabsorption occurs under normal circumstances (Cottle 1964; Galton and Nisula 1972).

The studies presented here describe the effect of reduced feed intake in the goat on the function of the thyroid gland and the excretion of its hormones. Since the goat is a common domestic animal in areas of the world where malnutrition of man and his domestic animals is endemic, these studies may assist in our understanding of the mechanism of adaptation of a domestic animal to malnutrition.

Materials and Methods

Animals

Eight closely matched young male British Alpine goats were weaned on pasture, and then 3 weeks later transferred to metabolism crates in a laboratory.

The diet consisted of lucerne pellets supplemented with a vitamin–mineral mixture (Sustavet-R, Briston Vet. Products, Crows Nest, N.S.W.). *Ad libitum* feed intake was permitted for 4 weeks, during the last 5 days of which feed intake was measured daily. The animals were weighed, and the feed supplied to two groups of three animals was reduced by 100 g/day until the groups reached 70 and 50% respectively of their *ad libitum* intake. These levels of feed were maintained for a further 2 days before the start of thyroid function evaluation, and throughout the 3 days of measurements. This procedure was carried out twice, once at 6 months and once at 7 months of age. Similar experiments restricting feed intake to 50 and 20% of *ad libitum* intake were carried out at 14 and 15 months of age. In each experiment, two control goats remained on *ad libitum* feed intake. All animals were weighed at the end of thyroid function measurement.

During the period of feed restriction 100 mg of KI was dissolved in each animal's drinking water daily, to supply iodide in excess of requirement. At the beginning of each experiment 25 μCi of [^{125}I]thyroxine was dissolved in 2 ml sterile saline and administered intravenously through the right jugular vein. Blood samples were taken at 12-h intervals up to 72 h by puncture of the left jugular vein. Total faecal and urine collections were made every 12 h up to 72 h.

Analysis of Faeces and Urine

Urine was assayed by the method of Irvine (1969) to determine [^{125}I]thyroxine. This method used human plasma as a source of thyroxine-binding globulin, and separated ^{125}I$^-$ and [^{125}I]iodotyrosine (if present) from [^{125}I]thyroxine through precipitation of the hormone–globulin complex. Total urine radioactivity was measured, as well as the extracted [^{125}I]thyroxine, by scintillation counting (Packard Gamma Spectrometer).

Faeces were dried at 70°C and ground in a mill. Aliquots of 0·5 g were used for radioactivity measurements. The ground material was twice washed with 5·0 ml distilled water, enabling inorganic iodide and a proportion of the thyroxine to be extracted (Blomstedt and Neujahr 1964). The thyroxine content of the aqueous extract was determined as described for urine. The radioactivity of the washed faeces was considered to be thyroxine and its conjugates and derivatives, and was added to the thyroxine determined in the aqueous extract. The radioactivity of faecal and urine samples was expressed as a percentage of the ^{125}I administered.

Determination of Thyroxine Turnover Rate

Total plasma thyroxine was measured by the method of Murphy (1965), as described previously (Falconer and Jacks 1975). Measurements of [^{125}I]thyroxine content were carried out on plasma samples collected as previously described. The method of Yousef and Johnson (1967, 1968) was employed, which measured [^{125}I]thyroxine bound to plasma proteins precipitated at 5% concentration of trichloroacetic acid. Turnover rate was determined from a graphical measurement of [^{125}I]thyroxine half life:

$$\text{thyroxine fractional turnover rate} = 0{\cdot}693/\text{half life (days)}.$$

Thyroxine distribution volume was determined by extrapolation of the plasma [^{125}I]thyroxine disappearance curve to zero time, when:

$$\text{distribution volume (litres)} = 100/\text{radioactivity in plasma thyroxine (\% dose per litre)}.$$

Thyroxine secretion rate was calculated from:

$$\text{thyroxine secretion rate } (\mu g/\text{day}) = \text{thyroxine distribution volume (litres)} \times \text{thyroxine concentration in plasma } (\mu g/l) \times \text{thyroxine fractional turnover rate } (\text{day}^{-1}).$$

Results

Urinary Excretion of Thyroxine and its Metabolites

The initial experiments were carried out at 100, 70 and 50% of *ad libitum* feed intakes. At 58 h after administration less than 10% of administered radioactivity had been excreted in the urine at any level of feed intake. No trend in urinary excretion was seen with variation of feed intake. The second experiments at 100, 50 and 20% of *ad libitum* feed intake gave results similar to the first experiments. Of the urinary ^{125}I excreted, the proportion of labelled thyroxine varied between 32 and 50% of the total, with no significant changes due to variations in feed intake.

Faecal Excretion of Thyroxine and its Metabolites

The excretion of radioactivity through the faeces was greater than through the urine. For comparison cumulative mean (±s.e.) excretion at 58 h after [^{125}I]thyroxine administration was calculated. In the first experiments $16\cdot9\pm2\cdot4$, $17\cdot2\pm2\cdot5$ and $16\cdot0\pm1\cdot2$% of the dose was excreted in the faeces in this period for 100, 70 and 50% of *ad libitum* feed intake respectively.

Calculation of the proportion of thyroxine radioactivity (or conjugate radioactivity) to total faecal radioactivity showed that only 7–13% of the total was $^{125}I^-$.

The second series of experiments carried out at 100, 50 and 20% of *ad libitum* feed intake showed significant ($P < 0\cdot02$) reduction in faecal excretion in animals fed only 20% of *ad libitum* intake. The mean (±s.e.) excretions up to 50 h were $26\cdot0\pm1\cdot0$, $23\cdot6\pm0\cdot2$ and $19\cdot9\pm1\cdot1$% of the dose administered for 100, 50 and 20% intake respectively. As recorded in the first experiments, a minor proportion of the faecal radioactivity was as $^{125}I^-$. By comparison to excretion in the urine, in which half or more of the radioactivity was free $^{125}I^-$, it is clear that the major route for thyroxine excretion is through the faeces. Excretion of iodide, by contrast, was largely through the urine.

Thyroid Function

Because the time interval between the first series of experiments and the second series was 7 months, during which time the animals continued to grow, it was possible to analyse the data for age and body weight as well as treatment effects. Statistical analysis by analysis of variance, and/or regression analysis was applied separately to each pair of experiments.

Plasma Thyroxine Concentration

Examination of the thyroxine concentrations of the control group of goats showed no significant changes with increasing age or body weight of animals (Table 1). Significant changes ($P < 0\cdot001$) with feed intake were seen in the second pair of experiments (Table 2) where mean plasma concentration decreased from $88\cdot7$ (control) to $74\cdot0$ μg/l at 20% of *ad libitum* feed intake.

Table 1. Relationship between thyroid function and weight or age in young goats fed *ad libitum*

	Mean values (Y)				(X)	Correlation coefficient	Significance (P)	Regression equation
Age (months)	6	7	14	15	—	—	—	—
Body weight (kg)	17·4	19·7	30·7	36·2	Age	0·980	$< 0·001$	$y = 1·89x+6·18$
Thyroxine distribution volume/body weight (l/kg)	0·35	0·23	0·27	0·15	Body weight	−0·586	*c.* 0·05	$y = -0·007x+0·44$
					Age	−0·546	*c.* 0·05	$y = -0·012x+0·37$
Thyroxine fractional turnover rate/day	0·68	0·64	0·89	0·82	Body weight	0·477	—	—
					Age	0·462	—	—
Plasma thyroxine concentration (µg/l)	85·7	82·8	88·0	89·4	Body weight	0·324	—	—
					Age	0·375	—	—
Thyroxine secretion rate (µg/day)	358	240	452	392	Body weight	0·582	$0·05 > P > 0·01$	$y = 6·69x+188$
					Age	0·592	$0·05 > P > 0·01$	$y = 13·5x+220$
Thyroxine secretion rate/body weight$^{0·75}$ (µg kg$^{-0·75}$ day^{-1})	42·6	26·7	34·0	27·0	Body weight	−0·390	—	—
					Age	−0·366	—	—

Table 2. Evaluation of thyroid function in feed-restricted goats

	Group	Mean values (Y) for feed intake (X) of: 100%	70%	50%	20%	Correlation coefficient	Significance (P)	Regression equation
Body weight (kg)	1	18·6	15·1	16·1	—	0·502	$0{\cdot}05 > P > 0{\cdot}02$	$y = 0{\cdot}005x + 12{\cdot}57$
	2	33·4	—	28·9	26·9	0·709	$< 0{\cdot}001$	$y = 0{\cdot}082x + 25{\cdot}1$
Thyroxine distribution	1	5·28	4·23	4·2	—	0·413	*c.* 0·1	$y = 0{\cdot}023x + 2{\cdot}91$
volume (litres)	2	5·61	—	4·44	4·05	0·794	$< 0{\cdot}001$	$y = 0{\cdot}02x + 3{\cdot}57$
Thyroxine distribution	1	0·29	0·28	0·27	—	0·188	—	—
volume/body weight (l/kg)	2	0·21	—	0·15	0·15	0·496	$0{\cdot}1 > P > 0{\cdot}05$	$y = 0{\cdot}0009x + 0{\cdot}13$
[^{125}I]Thyroxine	1	25·9	28·9	30·8	—	−0·480	*c.* 0·05	$y = -0{\cdot}1x + 35{\cdot}76$
half life (h)	2	19·7	—	21·4	25·8	−0·360	—	—
Thyroxine fractional turnover	1	0·660	0·587	0·550	—	0·562	$0{\cdot}02 > P > 0{\cdot}01$	$y = 0{\cdot}002x + 0{\cdot}436$
rate/day	2	0·853	—	0·787	0·656	0·375	—	—
Plasma thyroxine	1	84·2	89·9	80·6	—	0·193	—	—
concentration (μg/l)	2	88·7	—	81·4	74·0	0·868	$< 0{\cdot}001$	$y = 0{\cdot}175x + 71{\cdot}0$
Thyroxine secretion rate	1	299·0	224·8	181·2	—	0·754	$< 0{\cdot}001$	$y = 2{\cdot}65x + 38{\cdot}05$
(μg/day)	2	422·0	—	282·3	190·4	0·887	$< 0{\cdot}001$	$y = 2{\cdot}88x + 135{\cdot}0$
Thyroxine secretion rate/	1	33·4	29·4	22·5	—	0·695	$< 0{\cdot}001$	$y = 0{\cdot}23x + 11{\cdot}0$
body weight$^{0\cdot75}$ (μg kg$^{-0\cdot75}$ day^{-1})	2	30·4	—	22·9	16·1			

Thyroxine Fractional Turnover Rate

This parameter of thyroid function represents the proportion of the body pool of thyroxine replaced each day. Examination of changes in this rate with increasing age and body weight in the control group of goats showed a non-significant ($0\cdot 1 > P > 0\cdot 05$, Table 1) increase from 0·66 to 0·85 per day per animal comparing the mean rate for the first series of experiments with that from the second series.

Fractional turnover rate decreased with decreasing feed intake (Table 2) in both series of experiments, though only in the first series was this statistically significant ($0\cdot 02 > P > 0\cdot 01$).

Thyroxine Distribution Volume

This volume when expressed per unit body weight showed a marginally significant negative correlation with age and body weight ($P \simeq 0\cdot 05$, Table 1) in control goats, indicating that the proportion of body mass into which thyroxine distributes decreases with the size of animal. There was no significant direct correlation with body weight, though the mean distribution volume was higher in the older and heavier goats (5·28–5·61 litres).

Thyroxine distribution volume showed a decrease with decreasing feed intake which was particularly marked in the second series of experiments ($P < 0\cdot 001$, Table 2).

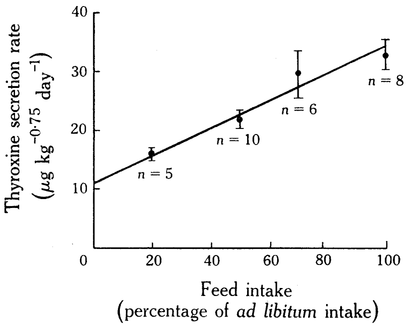

Fig. 1. Effect of restriction of feed intake on the thyroxine secretion rate of young male goats. Standard errors are shown by vertical bars.

Thyroxine Secretion Rate

Calculation of the thyroxine secretion rates per animal in *ad libitum* fed goats showed a significant increase with body weight or age ($P < 0\cdot 05$, Table 1). Thyroxine secretion rates calculated per animal also showed highly significant decreases with decreasing feed intake in both series of experiments ($P < 0\cdot 001$, Table 2). At 20% of *ad libitum* feed intake the mean thyroxine secretion rate was only 45% of the secretion rate of the *ad libitum* fed goats. Recalculation of these secretion rates per kilogram$^{0\cdot 75}$ body weight also demonstrated a very highly significant reduction with decreasing feed intake ($P < 0\cdot 001$, Fig. 1), showing that the decrease was not due to the reduced metabolic mass of the underfed animal.

Discussion

In starvation the removal of thyroid hormone from the blood is reduced, this reduction being brought about by possible decreases in hormone deiodination in the peripheral tissues, and decreased biliary–faecal excretion of hormone conjugates

(Nathanielsz 1970; Ingbar and Galton 1975). Changes in peripheral deiodination of [^{125}I]thyroxine, in animals provided with excess I^- through their drinking water, will be reflected by alterations of the urinary $^{125}I^-$ excretion. In these studies no significant changes in urinary $^{125}I^-$ were observed, indicating that peripheral deiodination of thyroxine remained essentially unaltered in goats restricted to 20% of *ad libitum* feed intake. This is in contrast to results in the rat where reduced peripheral deiodination of thyroxine has been shown during starvation (Nathanielsz 1970; Ingbar and Galton 1975).

A decreased loss of [^{125}I]thyroxine in the faeces was observed in the goats restricted to 50 and 20% of *ad libitum* feed intake; this was observed previously in rats and rabbits on restricted diets by Ingbar and Galton (1975) and Reichlin and Koussa (1958). This may be attributed to decreased faecal mass and hence reduced biliary secretion, since recent studies have not shown any net reabsorption to occur (Galton and Nisula 1972). It is apparent from the data presented earlier that faecal excretion is the major route of elimination of thyroxine in the goat.

The decrease in the fractional turnover rate of thyroxine with decreasing feed intake shows a reduction in the elimination of thyroxine from the blood at reduced feed intakes, due to either diminished deiodination or excretion of hormone. Since no variation in urinary $^{125}I^-$ excretion was observed, but a significant decrease in faecal excretion of [^{125}I]thyroxine at low feed intakes was recorded, the decreased rate of thyroxine turnover could be largely attributed to the reduction in loss by faecal excretion.

Thyroxine distribution volume is related to body size (Post and Mixner 1961) though in the present experiments no simple correlation was observed since the volume per kilogram decreased as body weight increased. Overall the heavier animals had a larger distribution volume as would be expected, and also showed a reduction in volume with decreased feed intake. This reduction was close to significance even when calculated as volume per kilogram, thereby removing the effects of lowered body weight which resulted from restricted feeding. It would appear likely that these changes in body distribution of thyroxine which occurred with restricted feeding may be due to a decrease in thyroxine binding capacity of the blood as has been seen in other studies (Schatz *et al.* 1967; Ingenbleek *et al.* 1974).

Further support for a possible reduction in thyroxine binding capacity of the blood is shown by the significantly decreased plasma thyroxine concentration observed in the goats restricted to 20% of *ad libitum* feed intake. This decrease in total circulating thyroxine has been observed in starved rats (Donati *et al.* 1963; Schussler 1966), but may occur with a constant concentration of free thyroxine in the plasma presumably due to decreased binding capacity.

Thyroxine secretion rate per kilogram$^{0 \cdot 75}$ body weight was shown to tend to decrease with increasing age and body weight in the goat, in a manner similar to that observed by Falconer and Robertson (1961) in the sheep. Feed restriction in both series of experiments resulted in significantly decreased thyroxine secretion rates per animal. Similar results have been reported for feed restriction in neonatal rats (Shambaugh and Wilber 1974), adult rats (Grossie and Turner 1962) and cattle (Post 1965). Whether the decreased rate of secretion from the thyroid observed during feed restriction can be considered due to a decrease in TSH secretion, or a lack of response of the thyroid to circulating TSH, or both, is unclear. In man subjected to protein-caloric malnutrition, and in protein-depleted rats, no changes in circulating

TSH were observed (Florsheim *et al.* 1970; Chopra and Smith 1975). However, normal thyroid responses to exogenous TSH were absent in severely malnourished rats or children, indicating that the gland becomes inactive in malnutrition and does not respond to exogenous stimulation (Cowan and Margossian 1966; Graham *et al.* 1973).

The calculated thyroxine secretion rate per kilogram$^{0 \cdot 75}$ body weight also showed a highly significant reduction with restricted feed intakes. The mean body weight of the goats in the second series of experiments was 33·4, 28·9 and 26·9 kg for 100, 50 and 20% of *ad libitum* feed intake respectively, which reflects both actual tissue weight alterations, and a reduced weight of digesta within the body in the feed-restricted animals. The magnitude of the reduction in thyroxine secretion rate per kilogram$^{0 \cdot 75}$ body weight (Fig. 1) at 20% of *ad libitum* feed intake would be expected to be of considerable physiological significance since the rate of catabolic processes during starvation is regulated by thyroid activity (Carter *et al.* 1975) just as metabolic rate in the fed animal is under the control of the thyroid gland (see Hoch 1974).

These studies have shown that the goat responds to restriction of feed intake by reducing the rate of secretion of thyroxine, by reducing the plasma thyroxine concentration, the distribution volume of thyroxine, the rate of degradation or loss of plasma thyroxine and the faecal excretion of thyroxine. These responses may be expected to result in reduced metabolic activity, which would be of survival value to the animal.

References

Blomstedt, B., and Neujahr, H. Y. (1964). Chromatographic studies on ^{131}I-compounds in faeces and bile. *Acta Endocrinol. (Copenhagen)* **14**, 373–482.

Carter, W. J., Shakir, K. M., Hodges, S., Faas, F. H., and Wymm, J. O. (1975). Effect of thyroid hormone on metabolic adaptation to fasting. *Metab. Clin. Exp.* **24**, 1177–83.

Chopra, I. J., and Smith, S. R. (1975). Circulating thyroid hormones and thyrotropin in adult patients with protein-calorie malnutrition. *J. Clin. Endocrinol. Metab.* **40**, 221–7.

Cottle, W. H. (1964). Biliary and faecal clearance of endogenous thyroid hormone in cold acclimated rats. *Am. J. Physiol.* **207**, 1063–6.

Cowan, J. W., and Margossian, S. (1966). Thyroid function in female rats severely depleted of body protein. *Endocrinology* **79**, 1023–6.

Donati, R. M., Warnecke, M. A., and Gallagher, N. I. (1963). The effect of absolute caloric deprivation on thyroid hormone synthesis and release in the rat. *Metab. Clin. Exp.* **12**, 833–6.

Falconer, I. R., and Jacks, F. (1975). Effect of adrenal hormones on thyroid secretion and thyroid hormones on adrenal secretion in the sheep. *J. Physiol. (London)* **250**, 261–73.

Falconer, I. R., and Robertson, H. A. (1961). Changes in thyroid activity during growth in sheep. *J. Endocrinol.* **22**, 23–30.

Florsheim, W. H., Suhr, B. Z., Mirise, R. T., and Williams, A. D. (1970). Thyroid function in protein-depleted rats. *J. Endocrinol.* **46**, 93–9.

Galton, V. A., and Nisula, B. C. (1972). The enterohepatic circulation of thyroxine. *J. Endocrinol.* **54**, 187–93.

Graham, G. G., Baertl, J. M., Claeyssen, G., Suskind, R., Greenburg, R. G., and Blizzard, R. M. (1973). Thyroid hormonal studies in normal and severely maladjusted infants and small children. *J. Pediatr.* **83**, 321–31.

Grossie, J., and Turner, C. W. (1962). Thyroxine secretion rates during food restriction in rats. *Proc. Soc. Exp. Biol. Med.* **110**, 631–3.

Hoch, F. L. (1974). Metabolic effects of thyroid hormones. In 'Handbook of Physiology', Section 7, Endocrinology, Vol. III, Thyroid, Ch. 23, pp. 391–411. (American Physiological Society: Washington, D.C.)

Ingbar, D. H., and Galton, V. A. (1975). The effect of food deprivation on the periferal metabolism of thyroxine in rats. *Endocrinology* **96**, 1525–32.

Ingenbleek, Y., De Nayer, Ph., and De Visscher, M. (1974). Thyroxine-binding globulin in infant protein-calorie malnutrition. *J. Clin. Endocrinol. Metab.* **39**, 179–80.

Irvine, C. H. G. (1969). Qualitive and quantitive aspects of thyroxine metabolism in sheep. *Endocrinology* **85**, 662–73.

Milner, R. C. G. (1972). Endocrine adaptation to malnutrition. *Nutr. Rev.* **30**, 103–6.

Murphy, B. P. (1965). The determination of thyroxine by competitive protein-binding analysis employing an ion-exchange resin and radiothyroxine. *J. Lab. Clin. Med.* **66**, 161–7.

Nathanielsz, P. W. (1970). The effect of diet and acute starvation on the deiodination of thyroxine and triiodothyronine in the thyroidectomized rat. *J. Physiol.* (*London*) **206**, 701–10.

Post, T. B. (1965). The effect of level of nutrition on thyroid activity in beef cattle. *Aust. J. Agric. Res.* **16**, 881–91.

Post, T. B., and Mixner, J. P. (1961). Thyroxine turnover methods for determining thyroid secretion rates in dairy cattle. *J. Dairy Sci.* **44**, 2265–77.

Reichlin, S. A., and Koussa, M. G. (1958). The effect of starvation and dehydration on radioiodine excretion following injections of I^{131} labelled thyroxine. *Endocrinology* **62**, 868–72.

Schatz, D. L., Sheppard, R. H., Palter, H. C., and Jaffri, M. H. (1967). Thyroid function studies in fasting obese subjects. *Metab. Clin. Exp.* **16**, 1075–85.

Schussler, J. (1966). Paradoxical effects of starvation and cortisone administration on free thyroxine concentration and thyroxine metabolism. *J. Clin. Invest.* **45**, 1072.

Shambaugh, G. E., and Wilber, J. F. (1974). The effect of caloric deprivation upon thyroid function in the neonatal rat. *Endocrinology* **94**, 1145–9.

Srebnik, H. H., Evans, E. S., and Rosenberg, L. L. (1963). Thyroid function in female rats maintained on a protein-free diet. *Endocrinology* **73**, 267–70.

Vagenakis, A. G., Burger, A., Portnay, G. I., Rudolph, M., O'Brian, J. T., Azizi, F., Arky, R. A., Nicod, P., Ingbar, S. H., and Braverman, L. E. (1975). Diversion of peripheral thyroxine metabolism from activating to inactivating pathways during complete fasting. *J. Clin. Endocrinol. Metab.* **41**, 191–4.

Van Middlesworth, L. (1975). Thyroxine excretion, a possible cause of goiter. *Endocrinology* **61**, 570–3.

Yousef, M. K., and Johnson, H. D. (1967). A rapid method for estimation of thyroxine secretion rate of cattle. *J. Anim. Sci.* **26**, 1108–12.

Yousef, M. K., and Johnson, H. D. (1968). Effects of heat and feed restriction during growth on thyroxine secretion rate of male rats. *Endocrinology* **82**, 353–8.

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