

Consequences of Nutritional Obesity on Thyroid Tissue (37415)

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(Introduced by T. D. Luckey)

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Several nutritional factors are known to influence thyroid activity and the effect of the thyroid on the organism; the early literature has been extensively reviewed (1). Drastic food restriction resulted in a resting condition of the thyroid (2). Goiters developed in rats which exhibited multiple deficiencies (3). Protein deficiency induced a resting condition of the thyroid (4) and a decrease of the protein-bound iodine content of the serum (5). In rats fed a low protein diet with possible multiple deficiency an intense lymphocyte infiltration of the thyroid was observed; this was comparable to thyroiditis (6). The thyroid was stimulated by feeding high fat (7-9) or high protein (10) diets. Addition of 30% casein of low iodine content to a goitrogenic meal diet prevented the increased size of the thyroid and induced a resting condition of the gland shown by the ratio of urinary and fecal iodine secretion (11). When iodine deficiency was avoided, vitamin deficiencies, such as avitaminosis A (12-14), polished rice disease (15), or thiamine deficiency (16, 17), induced a resting condition and atrophy of the thyroid. Scurvy was characterized by a stimulated condition of the thyroid (18, 19), possibly a consequence of a simultaneous vitamin P deficiency (20). Administration of excessive amounts of vitamin A (17, 21), ascorbic acid (22), or vitamin D (23) resulted in a resting condition of the thyroid, whereas thiamine administration stimulated the thyroid (24). The interaction between vitamins and thyroid is intricate; a mutual antagonism between thyroxine and vitamins or between thyrotropin and vitamins was reviewed (1).

A literature search revealed no description of the thyroid in nutritional obesity. This interrelationship became of special interest

when conspicuous changes of the thyrotropic cells of the anterior pituitary were observed in obese animals (6).

Methods. Expt I. Weanling male Wistar-Commentry rats¹ bred in our laboratory were housed for 130 days in individual metabolic cages (29 × 18 × 14 cm) and were fed a diet made of equal parts of evaporated whole milk (fat content, 7.5%) and commercial rat food. This food is a thick mash which can be swallowed by the rats without gnawing. Rats eat it quickly in great amounts (to 50 g daily). This was the parent (P) generation.

Expt II. The three heaviest males from Expt I were mated with twin sisters and Expt I was repeated with their male offspring. Again the heaviest subjects were selected for breeding. This was repeated in the generation F₂, F₃, F₄ and F₅.

Expt III. In every generation 16 rats were changed at 100 days to a "slimming" diet of commercial rat food (hard pellets) and carrots.

At regular intervals in each experiment, groups of four animals were injected intraperitoneally with 0.1 μCi of carrier-free Na¹³¹I. They were sacrificed with chloroform 2 hr later. Total body fat content was estimated by the density method (26). The left thyroid was fixed in Bouin's reagent for histologic examination. The ¹³¹I uptake of the right thyroid was measured with a well-shaped crystal counter. At corresponding intervals the same determinations were performed on control rats from the corresponding generation.

Results. The results of the fat analyses (27) are summarized as follows. In P genera-

¹ In agreement with Hollifield and Parson (25) we observed that female rats of their strain can not be fattened.

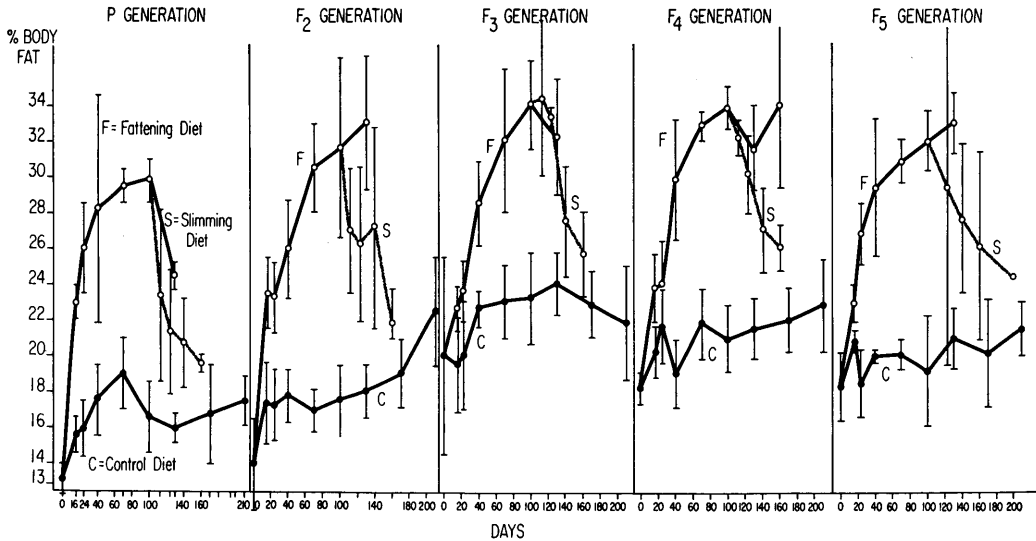


FIG. 1. Whole body fat content of rats fed control (C), fattening (F) and slimming (S) diets for 5 successive generations. Data indicate mean \pm 1 standard deviation for each period.

tion the total body fat content (Fig. 1) increase during 100 days to a maximum of $29.5 \pm 1.2\%$. It decreased from Days 100 to 130 to $24.5 \pm 0.8\%$ although the animals still received the "fattening" diet. In P generation only 6 of 105 animals fed the fattening diet increased in weight after Day 100. The three not selected for breeding had a body fat content of 32.6, 33.1 and 34.8%. In the following generations all rats continued to gain weight after Day 100; the average fat content of the "fattened" animals was 33% at 100 or 130 days in generations F_2 – F_5 . Thus, the average values in these generations correspond to the extremes in the P generation.

The "slimming" experiment demonstrated a further difference between the different generations. The decrease of the fat content was rapid in P where normal values were attained after 40 days of eating the "slimming" diet. In F_2 this result was obtained after 60 days; in F_5 it was not obtained within 95 days.

The results of the radioactivity determinations of the thyroid are summarized in Tables I and II. These data show:

1. In control rats ^{131}I uptake was decreased when compared to P; this is seen more in F_3 , F_4 and F_5 than in F_2 .

2. The ^{131}I uptake increased conspicuously

for a short time in overfed rats of the P and F_2 generations. This did not occur in the subsequent generations.

3. In all generations, as the experiment progressed, the ^{131}I uptake of overfed rats decreased more and more in each successive generation; this was generally true for "slimmed" rats; and

4. in "slimmed" rats of P and F_2 generations, after a transitory decrease, the ^{131}I uptake increased with time. In F_3 , F_4 and F_5 generations the ^{131}I uptake remained low, conspicuously so in F_5 .

The histological examination did not show conspicuous changes, except in short-term obese P and F_2 rats where evidence of an intense stimulation of the thyroid was found; the colloid was nearly completely resorbed, the epithelium was thick and exhibited frequent mitoses (4). In long-term experiments the thyroid has shown a picture of resting state (large follicles, flat epithelium).

Discussion. The data indicate that by selection a strain of rats could be obtained which were characterized by: (a) an increased possibility to become fat; (b) a decreased possibility to be slimmed down again; and (c) a decreased activity of the thyroid, which was more decreased by fattening. The changes of the thyroid can be compared with those reported for the anterior pituitary (6):

TABLE I. Radioactivity of Five Successive Generations of the Thyroid of Control (Ac) and Obese (Ob) Rats 2 hr After an Intraperitoneal Injection of $0.1 \mu\text{Ci}$ of Carrier-Free Na^{131}I .^a

Days	P			F ₂			F ₃			F ₄			F ₅		
	Ac	Ob	p	Ac	Ob	p	Ac	Ob	p	Ac	Ob	p	Ac	Ob	p
0	385 ± 17			313 ± 90			360 ± 26			394 ± 99			327 ± 39		
16	382 ± 42	904 ± 14	<0.001	519 ± 141	1521 ± 164	<0.001	325 ± 37	472 ± 35	<0.001	376 ± 80	262 ± 45	0.073	228 ± 22	214 ± 71	0.755
24	391 ± 22	643 ± 27	<0.001	425 ± 114	1015 ± 47	<0.001	325 ± 28	535 ± 42	<0.001	354 ± 100	286 ± 17	0.285	198 ± 9	206 ± 19	0.524
40	545 ± 20	391 ± 21	<0.001	448 ± 124	530 ± 90	0.385	375 ± 30	489 ± 13	<0.001	287 ± 35	219 ± 12	0.018	198 ± 22	188 ± 3	0.460
70	539 ± 42	323 ± 13	<0.001	376 ± 30	385 ± 39	0.770	328 ± 40	280 ± 39	0.265	275 ± 20	228 ± 6	0.008	162 ± 10	173 ± 10	0.22
100	525 ± 30	311 ± 67	<0.001	223 ± 30	256 ± 52	0.073	280 ± 50	185 ± 85	0.139	279 ± 30	208 ± 42	0.052	227 ± 57	168 ± 18	0.136
130	493 ± 35	359 ± 26	<0.001	227 ± 53	215 ± 85	0.845	237 ± 28	217 ± 46	0.533	249 ± 20	160 ± 33	0.006	254 ± 32	144 ± 23	0.001
160	487 ± 29			282 ± 30			229 ± 18			195 ± 17			248 ± 24		
210	333 ± 35			300 ± 68			181 ± 11			187 ± 11			277 ± 6		

^a Data are expressed as impulses per milligram per minute, mean of four animals ± standard deviation.

TABLE II. Radioactivity of the Thyroid of Slimmed Rats in Five Successive Generations 2 hr After an Intraperitoneal Injection of 0.1 μ Ci of Carrier-Free Na¹³¹I.^a

T ₂ ^b	P	F ₂	F ₃	F ₄	F ₅
0	311 ± 67	256 ± 52	185 ± 85	279 ± 30	168 ± 18
12	232 ± 16	159 ± 13	189 ± 22	264 ± 27	
24	245 ± 45	232 ± 19	346 ± 18	267 ± 30	221 ± 26
40	318 ± 52	340 ± 18	353 ± 68	196 ± 67	98 ± 12
60	342 ± 62	320 ± 34	231 ± 23	238 ± 33	75 ± 30
95	—	—	—	—	59 ± 13

^a Impulses per milligram and minute, mean of 4 animals ± standard deviation.

^b T₂ = days fed the "slimming" diet following 100 days of overfeeding.

1. During the "fattening" period a zone of small cells with dense nuclei and little cytoplasm (the "kernhaufen" of Romeis) could be observed in the pituitary of all animals. This zone became larger and larger from generation to generation. In F₅ it corresponded to about $\frac{2}{3}$ of the gland.

2. Parallel with the stop of the weight increase (Day 130 in P) an explosive development in number and size of the big chromophobes was observed. According to Racadot (28) these are the corticotropic cells. This change was not observed in F₄ and F₅.

3. In P and F₂ the δ (thyrotropic) cells increased intensely in number and size after 24 days of "slimming" diet. The somewhat delayed reaction of these cells (12 days after the appearance of big chromophobes) may account for the transitory decrease of the ¹³¹I uptake in these animals. In F₄ and in F₅ the thyrotropic cells seemed to undergo degenerative changes (6). Thus did the changes of the thyroid parallel those of the anterior pituitary gland in our experiments.

This indicated that by selection we obtained a strain of rats characterized by a decreased activity of the thyroid. This was demonstrated further by the absence of the initial increase of the thyroid activity on fattening diet (in contradistinction to the reaction of the animals of the original strain).

It may be objected that these changes did not result from simple overfeeding, but from the presence of antithyroid compounds in the diet. Indeed, both milk and carrots contain thyroxine antagonists, such as (in milk) cholesterol, unsaturated fatty acids, casein, vitamin A and (in carrots) the carotene, as the provitamin A. Still, all these compounds

are known to counteract the influence of circulating thyroid hormone and are devoid of a characteristic action on the thyroid itself [see Comsa (1), for a review]. Casein is also antigoitrogenic (11).

There is no evidence of a goitrogenic influence of any one of the diets used. Goitrogenic action is characterized by histological evidence of a stimulated state of the thyroid parallel with a decreased iodine uptake. We never saw a single case of this condition. Histological characteristics of the functional state of the thyroid are strictly parallel to the iodine uptake without exception.

In conclusion, the changes of the thyroid in our animals seemed to express an interaction of two influences: overfeeding and subsequent slimming. Overfeeding resulted at length in a decreased activity of the thyroid, as shown by the decreased iodine uptake and the histological picture. Slimming resulted in a progressive increase of the thyroid activity as shown by the gradual increase of the iodine uptake in P and F₂ generations. This tendency was exhibited in F₃ with no consistent change in F₄ and a decrease in F₅. The iodine uptake was low in F₃, F₄ and F₅ in control animals fed the standard diet when compared to that of P.

Summary. Nutritional obesity was obtained in rats by *ad libitum* overeating of a simple diet. In these animals, feeding a less rich food resulted in a quick loss of their increased fat content.

By selection a strain of rats could be obtained which (a) increase their fat content to amounts exceptional in the original strain, and (b) are less able to lose their increased fat content when subjected to the "slimming"

diet.

In obese animals the ^{131}I uptake of the thyroid was conspicuously decreased during the fattening period, nor did it increase when the animals were subjected to the "slimming" diet.

Observations on thyroid activity and histology parallel those previously made on the anterior pituitary histology of the same rats.

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