The first objection (the paucity of numbers in the experimental group) is more valid. It is to some extent offset by the homogeneity of the group. All the cadets were of the same age, of the same social class, and during the experimental period were living under identical dietetic conditions. Another factor which increases the value of the observations is the striking manner in which the change over of vitamin and control groups half-way through the experiment in each case resulted in a reversal of the behaviour of the groups. This obviously increases the significance of the separate sets of observations, but no allowance for this was made in the computation of the results. The two halves of the experiment were treated separately, as if a second group of 69 students had been used for the second half. Had this actually been the case the differences obtained might well have been due to selection; but this can hardly be the true cause, since the same students were merely interchanged.

Despite these objections we feel that this report may be of value in drawing attention to a possible method of assessing the optimal rather than the minimal requirements of vitamins in the diet. A diet containing less than the optimum amount of a particular vitamin, while not producing a deficiency disease, may nevertheless give rise to a suboptimal physiological state which will only be revealed by the application of physiological tests such as we describe.

Summary

The effects of adding supplements of vitamins A, C, and D to the diet have been studied over a period of five months in 69 cadets living in university halls of residence at Manchester.

The cadets receiving vitamin supplements were less susceptible to minor respiratory and gastro-intestinal complaints than those receiving control tablets which contained no vitamins.

The group receiving vitamins showed a greater increase in resting vital capacity and in breath-holding and endurance times, and had a faster resting pulse rate than the control group.

We wish to express our thanks to Glaxo Laboratories Ltd. for facilitating the supply of vitamin and control tablets and capsules.

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EFFECTS OF VITAMINS ON EXPERIMENTAL HYPERTHYROIDISM

BY

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The problem of the relationship between thyroid hormone and vitamins is of great importance for the proper therapeutic application of these substances in several diseases and also for the treatment of hyperthyroidisms—in particular, Graves's disease. The existing literature on the subject is so large that economy of space unfortunately makes it impossible to review it here, but it will be reviewed elsewhere. At the same time it is most contradictory, apparently because the following facts have not been taken into consideration by some of the workers:

1. Vitamins are food factors; therefore thyroid hormone, the chief function of which is to increase the oxidation processes in the organism, increases the metabolism of the vitamins in a similar way to that, for example, of proteins, fats, and carbohydrates. Thus depletion of *vitamin A* in the organism of animals by thyroid hormone administration has been found by Abelin (1933), Parhon and Werner (1935), Sure and Buchanan (1937), and Mlinko (1938); a similar condition in hyperthyroid patients was indicated by Wohl and Feldman (1938). With regard to *vitamin B*, of especial importance are experiments by Himwich, Goldfarb, and Cowgill (1932), Hendricks (1933),

Cowgill and Palmieri (1933), Cowgill (1934), and Drill (1938), who showed that the requirement of vitamin B of an organism per unit of mass is proportional to the metabolism of that mass, and that thyroid hormone therefore greatly increases this requirement. The depletion of *vitamin C* from the animal organism by thyroxine has been recorded by Demole and Ippen (1935), Plaut and Bülow (1935), Mosonyi (1935), Nespor (1936), Sure and Theis (1938), and Thaddea (1938). Increase of metabolism due to any cause accordingly requires increased administration of vitamins: e.g., in the case of muscular work, Cowgill (1934) found this for vitamin B and Hamel (1937) for vitamin C.

2. Therefore when even non-toxic doses of thyroid hormone are given or mild hyperthyroidism is present without a corresponding increase in vitamin administration, a relative vitamin deficiency might develop with more or less pronounced symptoms of anorexia, partial starvation, and loss of body weight.

3. For these reasons it is difficult to draw definite conclusions as to the antagonistic effects of thyroid hormone and vitamins from the experiments of several previous workers who used, often deliberately, a diet deficient in, or containing only a minimal normal amount of, the vitamin investigated, or used toxic doses of thyroid hormone.

The effects produced by any substance differ greatly according to whether toxic or non-toxic doses are used. In toxicosis, non-specific, mostly destructive, changes occur which obscure the specific changes. This is true both for thyroxine and for vitamins.

Technique

Non-toxic Experiments.—All these facts were taken into consideration when planning our experiments (see Tables I and II), performed on rats kept on our usual diet. This diet is rich enough in all vitamins to ensure (this appears to be the best test) excellent breeding results. We have chosen as criteria for judgment of antagonism or co-operative activity the changes in body weight and weights of most of the organs, fat deposition, and histological structure of thyroid gland. We have used non-toxic doses both of thyroid hormone and of vitamins, but in the case of vitamins, except with vitamin D, they were much above the normal requirement, while with thyroid hormone they were large enough to produce specific and typical changes (Korenchevsky and Hall, 1941).

Experiments were performed on 121 male rats for investigation of the effects of vitamins B and C, and on 66 female rats for investigation of vitamins A and D. The final age of the rats averaged 150 days. Each experiment was repeated twice. Although the doses and, in the case of vitamin B complex, the numbers of vitamins B used were somewhat different in the first and second experiments, the results were similar. The data from both experiments were therefore pooled, and average figures only are given in Tables I and II.

TABLE I.—Effects of Non-toxic Hypervitaminosis A and D on the Means of Body Weight, Fat Deposition, and Actual Weights of Organs in Normal Female Rats and in Rats treated with Non-toxic Doses of Thyroid Hormones*

Organs	Co-V	Co+V	Thy-V	Thy+V
	Group 1	Group 2	Group 3	Group 4
Ovaries, mg.	68	68	87	84
Preputial glands, mg.	94	85	139	132
Adrenals, mg.	50	52	75	77
Thymus, g.	288	332	289	273
Liver, g.	7.05	7.03	9.57	9.64
Kidneys, g.	1.29	1.32	2.12	2.11
Spleen, mg.	729	674	1,002	1,226
Heart, mg.	714	712	1,028	1,036
Abdominal fat, g.	7.4	7.6	1.6	1.7
Final body weight, g.	196	195	188	186
Gain in body weight, g.	52	51	43	38
No. of rats in group	16	16	16	18

* In this and the following table "Co-V" denotes the group of control rats receiving no additional substances; "Co+V" the group of rats receiving an extra amount of vitamins; "Thy-V" the group of rats receiving thyroid hormone alone; "Thy+V" the group of rats receiving simultaneously thyroid hormone and an extra amount of vitamins.

No changes in weight of uterus, vagina, thyroid, hypophysis, and brain were obtained in this experiment.

The doses used were as follows: In the first experiment 85 mg. of desiccated thyroid in the form of a sweetened emulsion was given orally by pipette 3 times a week; and 0.6 mg. of thyroxine

* Dr. Korenchevsky desires to express to the University of Oxford and to Prof. E. S. Goodrich his own and the Lister Institute's gratitude for the kind hospitality extended to him and his co-workers in the Department of Zoology and Comparative Anatomy.

was injected subcutaneously twice a week. In the second experiment desiccated thyroid only was given, but in a larger dose—180 mg. for the first month of the experiment and 280 mg. for the rest of the experiment—6 times a week. Vitamins A and D were given orally in the form of halibut-liver oil diluted with cod-liver oil, the daily dose (4 drops by pipette) containing

aneurin, pyridoxine, and calcium pantothenate. The doses were also the same, except the dose of aneurin injected, which was raised to 1 mg. The rats of group 4 received in addition yeast and wheat germ (incorporated in the diet in the same proportions as in our original diet) either alone or plus the same amount of crystalline vitamins B as in group 3.

TABLE II.—Effects of Hypervitaminosis B (Groups 1-4) and C (Groups 5-8) on the Means of Body Weight, Fat Deposition, and Actual Weights of Organs in Normal Male Rats and in Rats treated with Non-toxic Doses of Thyroid Hormone *

Organs	Effect of Vitamins B				Effect of Vitamin C			
	Co-V	Co+V	Thy-V	Thy+V	Co-V	Co+V	Thy-V	Thy+V
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
Seminal vesicles, mg.	727	822	620	558	646	711	481	459
Prostate, mg.	935	1,010	803	815	911	939	731	702
Preputial glands, mg.	128	110	138	146	116	105	147	144
Adrenals, mg.	23	24	45	45	35	34	47	47
Thymus, mg.	290	273	243	199	298	268	233	255
Liver, g.	9.68	10.79	10.66	9.99	9.80	10.29	11.31	10.43
Kidneys, g.	1.88	2.02	2.71	2.47	1.93	1.91	2.75	2.48
Spleen, g.	991	1,109	1,611	1,439	982	1,137	1,591	1,434
Heart, mg.	928	976	1,289	1,235	949	939	1,290	1,234
Abdominal fat, g.	8.1	10.2	4.3	3.4	9.0	9.7	3.4	3.5
Final body weight, g.	268	285	242	230	272	270	239	237
Gain in body weight, g.	77	93	48	48	93	93	59	55
No. of rats in group	15	16	17	16	13	14	15	15

* No changes in weight of testes, penis, thyroid, hypophysis, and brain were obtained.

1,300 I.U. of vitamin A and 70 I.U. of vitamin D, 6 times a week in both experiments.

In the first experiment vitamins B were given orally in the form of a sweetened emulsion 6 times a week, the daily dose being: aneurin 0.22 to 0.5 mg., riboflavin 0.22 to 0.5 mg., nicotinic acid 2.2 to 5 mg. In the second experiment the same vitamins B and doses were given by mouth, with in addition subcutaneous injections 6 times a week, each dose containing 0.4 to 0.5 mg. aneurin, 0.5 mg. pyridoxine, and 1.5 to 2 mg. calcium pantothenate. In both experiments 20 mg. of vitamin C was given orally by pipette 3 to 6 times a week, and in addition 25 to 40 mg. was injected subcutaneously 6 times a week. The duration of the first series of experiments was 53 days and of the second 47 days.

Toxic Experiment.—An additional experiment was performed on 18 male rats (Table III) in order to discover in particular

TABLE III.—Effects of Hypervitaminosis B on the Means of Body Weight, Fat Deposition, and Actual Weight of Organs in Male Rats treated with Toxic Doses of Thyroxine

Organs	Controls	Thyroxine 1 mg. Daily			
		Alone	+ Crystalline Vits. B	+ Cryst. Vits. B + Yeast + Wheat Germ	
	Group 1	Group 2	Group 3	Group 4	
Testes, g.	2.81	2.58	2.24	2.61	
Seminal vesicles, mg.	934	361	487	408	
Prostate, mg.	712	397	452	486	
Penis, mg.	294	241	234	271	
Adrenals, mg.	24	36	33	16	
Thyroids, mg.	20	130	156	120	
Thymus, mg.	250	170	7.84	8.19	
Liver, g.	9.36	6.78	1.99	2.33	
Kidneys, g.	1.65	1.91	1.454	1.106	
Spleen, mg.	834	757	1,019	1,073	
Heart, mg.	818	1,058	1,4	1.3	
Abdominal fat, g.	4.2	1.4	1.4	1.3	
Final body weight, g.	215	152	174	176	
Gain (+) or loss (-) in body weight, g.	+63	-4	+17	+14	
No. of rats in group	5	4	4	5	

whether different effects are produced by thyroid hormone and vitamins B when (as in most experiments of previous workers) toxic doses of thyroid hormone are given to animals fed on a diet deficient in or containing a minimal normal amount of vitamins.

The diet was the same as that used in the non-toxic experiments but made considerably poorer in vitamin B complex by the exclusion of yeast and wheat germ, which were replaced by bread, and the substitution of rolled oats only for the grain mixture. One mg. of thyroxine was injected daily for 12 days, the rats being killed on the fourteenth day. To the rats of group 3 (Table III) the same vitamins B were given as in our second experiment: aneurin, riboflavin, and nicotinic acid by mouth, supplemented by subcutaneous injections of

All changes obtained were statistically analysed by one of us (B. Clapham) by means of Fisher's t-test. Unless they are mentioned as being "statistically not significant," all the results obtained were found to be statistically significant.

Experimental Hyperthyroidism

Non-toxic Hyperthyroidism.—The following changes, all statistically significant, were observed after administration of non-toxic doses of thyroid hormone (compare, in Table I, group 3 with group 1, and in Table II, groups 3 and 7 with groups 1 and 5): decreased gain in body weight and fat deposition, hypertrophy of adrenals, liver, kidneys, spleen, heart, and preputial glands in both sexes; hypertrophy of ovaries in females; and small decrease of seminal vesicles and prostate in males. Histological changes in the thyroids demonstrated a strong depressing effect on their function (flattened epithelium, accumulation of solid colloid in enlarged follicles). A preliminary histological examination of ovaries, adrenals, liver, kidneys, spleen, and heart confirmed our conclusion suggested by the increase in weight of these organs—namely, that thyroid hormone has a stimulating hypertrophying effect on them. A detailed microscopical investigation, however, might show new facts; it will be described elsewhere. Thus non-toxic doses of thyroid hormone simultaneously increased both anabolism (shown by hypertrophy of several of the organs) and katabolism (decreased gain in body weight and fat deposition), the anabolic processes prevailing over the katabolic. Although the treated animals were thinner than the controls they had the appearance of perfectly healthy animals.

Thyroid hormone therefore has hepatotropic, nephrotropic, and cardiotropic properties similar to those of androgenic hormones (Korenchevsky and Ross, 1940; Korenchevsky, Hall, Burbank, and Cohen, 1941), but its effect on adrenals appears to be different from that of androgens (Hall and Korenchevsky, 1938). The effect of simultaneous administration of thyroid and androgenic hormones should be investigated with the object of determining whether they might be used for therapeutical purposes in suitable diseases of liver, kidneys, and heart. Epstein (1922, p. 186), for example, obtained "striking" favourable results after the treatment of chronic parenchymatous nephrosis with thyroid hormone.

Toxic Hyperthyroidism.—The administration of toxic doses of thyroid hormone was followed by an atypical reaction (compare group 2 with group 1, Table III): loss of body weight, much greater atrophy of seminal vesicles and prostate and considerably less hypertrophy of kidneys, atrophy instead of hypertrophy of liver and spleen, decrease of testes, and pronounced involution of thymus. At the same time all the animals became weak and emaciated; their fur became dull, rough, and dirty; most rats suffered from diarrhoea and began to lose weight; and some died from thyrotoxicosis before the end of the experiment. Histologically the same depression of thyroid function was observed as with non-toxic doses. Thus

in general, instead of the predominant typical anabolic and hypertrophic reaction (still preserved only in adrenals and heart), with toxic doses katabolic and atrophic changes prevailed, resulting in some cases in the death of the animals.

Effect of Hypervitaminosis

The administration of the extra amounts of vitamins produced no considerable effects, if any (compare group 2 with group 1, Table I; and groups 2 and 6 with groups 1 and 5, Table II). Hypervitaminosis B and C (Table II) produced in male rats a small, consistent, but statistically not significant increase of seminal vesicles, liver, and fat deposition. Vitamin B also produced greater gain in body weight and improvement in external appearance and behaviour (the rats appeared to be more lively and, when handled, felt firmer and stronger, and had thicker and more glossy fur than the control groups "Co-V"). Histologically no definite effect of these doses of vitamins could be found on the structure of the thyroid gland, except perhaps a slightly depressing effect of halibut and cod-liver oils. This could easily be explained by the extra amount of iodine given in these oils (Mellanby, 1934; Sampson and Korenchevsky, 1932).

Effect of Hypervitaminosis on Hyperthyroidism

The effect of hypervitaminosis on non-toxic hyperthyroidism (group 4 in Table I, and groups 4 and 8 in Table II) was different from that on toxic hyperthyroidism (groups 3 and 4, Table III). In rats kept on our *normal diet and receiving non-toxic* doses of thyroid hormone, vitamins A and D (in the doses given) did not at all affect the specific reaction of organs and tissues to this hormone, while vitamins B and C produced a slight decrease in the hypertrophy of liver and kidneys. In rats kept on a *minimal normal* amount of vitamins B (Table III) and injected with *toxic* doses of thyroxine, the simultaneous administration of extra amounts of vitamins B was followed by a gain instead of a loss in body weight and the partial restoration of specific anabolic changes instead of a pathological (atrophic and almost exclusively katabolic) reaction of the organs to thyroid hormone. In such animals the atrophic changes were decreased in seminal vesicles, prostate, and liver and replaced by hypertrophy in spleen, while in kidneys hypertrophy became more pronounced. The fact that some typical reactions to thyroxine were not prevented in such animals indicates that in vitamin-treated rats suffering from thyrotoxicosis all the improvements described both by previous workers and by ourselves (including gain instead of loss in body weight) could be explained by the making good of the relative vitamin deficiency produced by, and complicating, the thyrotoxic effects. Histologically the thyroid glands were in the same resting condition as in the rats treated with thyroid hormone alone.

The results of our experiments therefore indicate that for the investigation of antagonistic effects neither toxic doses of thyroxine, which greatly raise the vitamin requirements and produce non-specific changes, nor diets with inadequate levels of vitamin content appear to be suitable.

Conclusions

In the therapeutical application of thyroid hormone its katabolic properties in raising metabolism and especially in reducing body fat are often taken most into consideration.

The results of our experiments (as judged by changes in weights and histological structure of organs) and those of some previous workers emphasize that thyroid hormone also possesses anabolic properties, which can lead to better development of such vital organs as liver, kidneys, spleen, heart, and adrenals in both sexes, and ovaries in females.

As shown especially in our experiments on females, it is possible, using moderate doses of thyroid hormone, to reduce the body fat to about one-fifth without affecting appreciably the gain in body weight, and at the same time preserving the stimulating anabolic effects of this hormone on the development of the vital organs mentioned above.

Thus from small or moderate doses of thyroid hormone favourable therapeutical results can be expected, but when large doses are given the useful effects disappear and the hormone becomes atypically toxic and dangerous.

The useful effects of thyroid hormone cannot be normally and fully operative, unless liberal amounts of vitamins are given simultaneously, because of the increased requirements

in vitamins which arise during conditions accompanied by increased metabolism (such as those produced by thyroid hormone).

Therefore the best possible therapeutical results can be expected from simultaneous administration of thyroid hormone with extra amounts of vitamins.

Since both thyroid hormone and male sex hormones possess hepato-, nephro-, and cardiostrophic properties, and thyroid hormone also produces ovario-, spleno-, and adrenostrophic effects, the possibility of therapeutical application of thyroid hormone in cautious doses with vitamins, or together with sex hormones, should be investigated in some suitable diseases of liver, kidneys, and heart, or when an increased activity of ovaries, adrenals, or spleen is desirable.

The results of our experiments and those of some previous workers do not suggest, as has been stated by certain authors, any direct antagonistic effects of vitamins on thyroid hormone; but the data indicate that some beneficial results of the administration of vitamins in some cases of experimental and clinical hyperthyroidism were probably due chiefly to removal of the relative vitamin deficiency present in these cases.

Grants from the Medical Research Council and the Lister Institute have enabled us to carry out this work, and to them we offer our thanks. We are also grateful to the Ella Sachs Plotz Foundation for a grant from which some of the technical expenses were met. We are indebted to Messrs. Roche Products Ltd. for the generous supply of vitamins, and to Messrs. Parke, Davis and Co. for the liberal supply of desiccated thyroid powder.

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THE INCREASING IMPORTANCE OF ENDOCRINOLOGY IN GENERAL MEDICINE*

BY

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In this address I hope to be able to indicate clearly that the "increasing importance of endocrinology in general medicine" is a reality and is of interest to the physician, surgeon, and gynaecologist, and therefore to the general practitioner.

Adrenal-Pituitary Disorders

Cushing's Syndrome.—I shall first consider a syndrome which has been brought into prominence in the last decade by the observation of Harvey Cushing (1932), but which had already been recognized and described as the "fat bearded diabetic woman" by Achard and Thiers. The eponymous title was suggested by Parkes Weber, who had himself previously given a magnificent clinical description of the disorder. Cushing's invaluable contribution was to draw attention to the possibility of a basophil adenoma of the anterior pituitary being a primary cause, comparable to the eosinophil adenoma of acromegaly. It is now recognized that other primary causes exist—namely, tumours of the adrenal cortex, of the ovary, and of the thymus

* Delivered as the Annual Oration to the Leeds Jewish Hospital Medical Society, Nov. 29, 1942.