Nutrition and Hormones

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and
HORMONES

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CHARLES C THOMAS · PUBLISHER

Springfield · Illinois · U.S.A.

CHARLES C THOMAS · PUBLISHER
BANNERSTONE HOUSE
301-327 EAST LAWRENCE AVENUE, SPRINGFIELD, ILLINOIS

Published simultaneously in The British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD., OXFORD, ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS, TORONTO

FIRST PRINTING

Printed in the United States of America

NUTRITION and HORMONES

Publication Number 11

AMERICAN LECTURE SERIES

A Monograph In

AMERICAN LECTURES IN ENDOCRINOLOGY

Edited by

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CONTENTS

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Introduction

THE ENDOCRINE glands are specific chemical factories upon which the whole organism depends. But, like all factories, their ability to produce useful products depends on the raw materials they receive. In discussing the relations between nutrition and the endocrine system, therefore, we are dealing with the relationship between raw materials and manufactured products.

Not only does the subject cover this problem, but both the products of the endocrine system and the foods themselves are used as essential materials in certain cells. Thus nutritive effects on the endocrine system may indirectly affect the function of other tissues. A properly controlled experiment in nutrition must distinguish between the direct results of the nutritive change and those mediated through the endocrine system. Conversely, a study of the metabolic effects of the hormones must take into consideration any change in food intake which itself would influence metabolism in the body. In medicine this interplay should be kept constantly in mind both in diagnosis and therapy.

Problems in nutrition cannot be approached without at the same time considering the rôle of hunger. How is it controlled? The regulation of hunger by the hypothalamus was first clearly demonstrated by Smith (1) in rats. He found that obese rats were not obtained if the hypophysis alone was removed; but if the hypothalamus was also damaged, obesity resulted. He then proceeded to damage the hypothalamus, leaving the hypophysis intact, and found that obesity still occurred. The same result has been observed in dogs, monkeys, and cats. Brobeck, Tepperman and Long (2) showed that the obesity was primarily due to increased food intake. If the food given the animals was limited to that of normal rats, there was no obesity. However, the animals with hypothalamic damage would eat the normal amount of food in a very short time. *The hypothalamus, therefore, appears to contain a center which depresses hunger.*

Another important observation which Long and his co-workers (3) made is that the rate at which food is eaten affects its utilization. Normal animals eat small amounts of food throughout the day. Rats were trained by Long to eat their entire daily ration in a two-hour

period. These animals gained more weight on the same amount of food than did those rats which ate throughout the day. This illustrates *the importance of eating habits* in influencing the interpretation of nutritional problems.

The tone of the gastric musculature is also an important regulator of hunger. The decreased food intake in thiamine-deficient rats appears to be due to the decreased tone of the gastro-intestinal musculature (4). If an animal is fed a thiamine-deficient diet by stomach-tube in quantities adequate to maintain normal growth when thiamine is added, there is a gradual swelling of the abdomen until the animal dies because the greatly distended stomach interferes with the circulation and the respiration. Very little of the food passes from the stomach into the intestine. In thiamine-deficiency, therefore, the loss of hunger is a compensatory phenomenon due to the decreased tone of the gastric muscle.

Increased energy expenditure also seems to stimulate hunger. This is seen, of course, in every growing animal. An example of loss of this stimulus is in the animal (including the human) with pituitary destruction but an intact hypothalamus (5). Such an individual has a decreased food intake but, if it is forced to consume normal amounts of food, the material is absorbed and the excess deposited as fat (Table 1). Stimulating growth in such an animal by injection of pituitary hormones will also stimulate the desire for food. In understanding the interplay between the hormones and nutrition, the effects on hunger and on eating habits must, therefore, be distinguished from those acting directly on the fundamental metabolism.

Pancreas

The relation between the endocrine system and nutrition was perhaps first clearly recognized with the demonstration of the internal secretion of the pancreas. In the total absence of insulin, carbohydrate is largely lost in the urine, protein is rapidly broken down, and the disturbances in the utilization of carbohydrate lead to utilization of fat by the most rapid means possible: its conversion into acetone bodies by the liver and their oxidation by the cells of the tissues in general. Some glucose is still used by the tissues of diabetic animals, but many workers do not agree with Soskin (6) that at ordinary diabetic blood

sugar levels the consumption of glucose represents as great a proportion of the metabolism as in normal animals. A large part of the energy is furnished by the circulating acetone bodies.

The administration of *insulin* definitely increases the utilization of glucose and its conversion to muscle glycogen, while it decreases

TABLE 1. CALORIC BALANCE ON YOUNG FORCE-FED RATS WITH AND WITHOUT THE HYPOPHYSIS

Rat Number	4	5	7	8	10	11
Type of preparation	Hypophysectomized	Control	Hypophysectomized	Control	Hypophysectomized	Control
Days on diet	22	22	32	32	54	54
Total intake, calories	725.4	745.1	1053.9	1053.9	1822.5	1822.5
Unabsorbed food, calories						
Carbohydrate	27.5	19.3	37.8	27.3	74.0	47.2
Protein	21.5	14.6	24.3	17.5	41.1	25.9
Fat	72.1	50.9	65.2	47.4	138.9	86.3
Total unabsorbed calories	121.1	84.8	127.3	92.2	254.0	159.4
Increase in N stored calories	6.9	34.2	16.2	33.4	17.9	61.4
Increase in fat stored calories	96.7	80.6	245.2	34.1	398.9	81.6
Total caloric increase	103.6	114.8	261.4	67.5	416.8	143.0
Calories used	500.7	545.5	665.2	802.0	1155.7	1520.1
Total metabolic rate Cal./day	22.8	24.8	20.8	25.1	21.4	38.2
Total metabolic rate* Cal./sq. m./day	10.3	10.7	10.0	11.6	9.3	12.1

* This is not basal metabolic rate, but the average total calories used in a day. (L.T. Samuels, R. M. Reinecke and K. L. Bauman, *Endocrinology* 33: 87, 1943.)

gluconeogenesis from protein. Price, Cori and Colowick (7) have been able to demonstrate in simple systems one means by which insulin brings about this effect. They have shown that a pituitary extract decreases the catalytic activity of hexokinase whereby circulating glucose is converted into phosphorylated glucose in the muscle and thence into glycogen. Insulin introduced into the simple system of hexokinase - glucose - adenosine triphosphate - pituitary extract inhibits the action of the pituitary hormone (Figure 1). Rice and Evans (8) also have published evidence that, in simple systems, insulin will increase the oxidation of pyruvic acid.

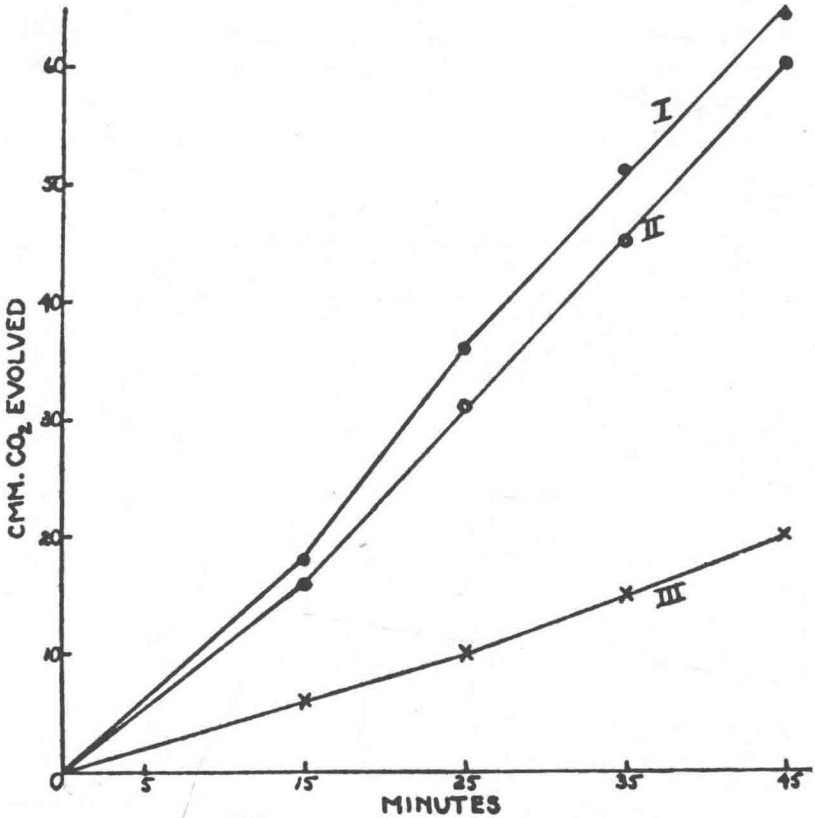

FIG. 1. The effect of anterior pituitary extract (K fraction) and insulin on purified muscle hexokinase.

The hexokinase activity is measured manometrically. The disappearance of adenosine triphosphate was determined chemically at the end of the experiment and was found to be in agreement with the results obtained by the manometric procedure. Curve I, hexokinase; Curve II, hexokinase 400 gamma APE 75 gamma insulin; Curve III, hexokinase 400 APE.

(W. H. Price, C. F. Cori and S. P. Colowick: *J. Biol. Chem., 160:*633, 1945.)

We have here then a substance which greatly influences the utilization of one of the major foodstuffs. This was recognized many years ago; and until the discovery of insulin, the only means by which diabetes could be even partially controlled was by a great reduction in the amount of carbohydrate in the diet. At the same time the

acidosis, due to increased utilization of fat by means of acetoacetic and beta-hydroxy butyric acid, required careful control. With insulin available, however, the ability to utilize carbohydrates can be restored.

The problem of maintaining nutrition in controlled diabetics remains, for there appears to be a quantitative relation between the amount of insulin and the carbohydrate which can be utilized. The most desirable level of carbohydrate in the diet and the level at which blood sugar should be maintained by insulin are still subjects of debate between specialists in this field, and most workers still control mild diabetes by reduction in carbohydrate intake.

Associated with the decreased utilization of carbohydrate in the insulin-deficient individual is a decreased need for the accessory factors associated with carbohydrate metabolism. Thiamine, niacin, and perhaps pantothenic acid act as coenzymes in carbohydrate oxidation systems. The need for these vitamins is reduced in the diabetic just as it is in the normal animal on a high fat, low carbohydrate diet. On administration of insulin the intake of the vitamin B complex should be high, since tissue concentrations must be restored as well as providing for the increased utilization as carbohydrate is metabolized.

Not only is the need for vitamins of the B complex dependent on the available insulin, but the effectiveness of insulin appears to be influenced by any deficiency of these factors. Martin (113) found that depancreatized dogs on a vitamin B-deficient diet became resistant to insulin. Elsom, Lukens, Montgomery and Jonas (114) found a progressive decrease in the response to insulin as deficiency of the B complex was produced experimentally in a woman (Table 2). On feeding riboflavin and thiamine, the subject became abnormally sensitive to insulin. Biskind (9) feels that vitamin therapy is effective in decreasing the hormone requirement of insulin-resistant diabetes.

There are certain dangers in the dietary control of diabetes. The pituitary gland is sensitive to both caloric and protein deficiencies. Limitation of food intake on a restricted diet, coupled with the increased protein breakdown associated with insulin deficiency, may lead to secondary disturbances in gonadal function and in growth because of pituitary insufficiency. This is particularly true during the

adolescent period. Two cases illustrating this condition are given in the section on the pituitary gland.

Excessive insulin production leads to the opposite effect on nutrition. There is a constant demand for carbohydrates to maintain the blood sugar level. The excess glucose not converted into glycogen and oxidized is converted into fat. All phases of carbohydrate metabolism are accelerated. As a consequence, along with the increased need

TABLE 2. BLOOD SUGAR, BEFORE AND FOLLOWING THE SUBCUTANEOUS ADMINISTRATION OF 2.5 UNITS OF INSULIN IN THE DIFFERENT EXPERIMENTAL PERIODS ON FEMALE SUBJECT, AGE SIXTY YEARS

Date 1938	Blood Sugar						
	Initial	½ hour	1 hour	2 hours	3 hours	Maximal decrease in blood sugar*	
	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	per cent	
March 11	71	66	56	59	61	21	Deficient diet
March 25	70	70	63	68	78	10	
April 29	66	76	66	70	76	0	
May 6	77	53	49	56	62	36	Deficient diet+thiamin
May 13	66	64	65	65	66	3	
May 17	68	61	59	58		15	
May 27	86	58	44	52	56	49	Deficient diet+thiamin+riboflavin
May 31	131	101	67	48	62	63	

* Maximal decrease in blood sugar is here represented as the per cent fall from the initial blood sugar to the lowest value obtained in the test.

(K. O. Elsom, F. D. W. Lukens, *J. Clin. Investigation* 19: 153, 1940.)

for carbohydrate there is an increased need of thiamine, niacin, and other accessory factors associated with carbohydrate metabolism. Thiamine deficiency can develop in such individuals when the intake would be ample for a normal person.

The work of Best, Haist, and Ridout (10) has established the importance of the diet in regulating the production of insulin by the pancreas. Apparently a high fat diet, fasting, or insulin administration lowers the insulin content of the pancreas below that on a high

carbohydrate diet alone. High protein diets give intermediate values. The conclusion seems justified that the carbohydrate available in the diet determines the production of insulin by the normal islet cells of the pancreas. Malignant cells of islet origin are apparently less susceptible to changes in carbohydrate level.

If insulin production is stimulated to too high a level, the islet cells may be exhausted. Lukens (11) has shown that this occurs when large doses of anterior pituitary diabetogenic extract are given to partially depancreatized rats. Houssay (12) has demonstrated the same effect in rats when total catabolism, and therefore conversion of protein to glucose, has been increased by administration of thyroid hormone. In neither of these cases, however, were the investigators able to obtain exhaustion diabetes in rats with completely normal pancreases.

The rôle of the vitamins in insulin production is still uncertain. The problem which arises in much of this type of work is to distinguish the effect of general inanition from that of the vitamin. In the case of thiamine, reduction in insulin production accompanies deficiency, but this was found to be due to the inanition rather than thiamine *per se* since animals limited to the same food intake but receiving ample thiamine showed a similar drop in insulin content (10). The insulin content of the pancreas of ascorbutic guinea pigs is reported to be reduced to one-eighth of the normal (13, 14), but no control of food intake by paired feeding is reported. An excellent review of the effect of diet on the insulin content of the pancreas has been published by Haist (15).

Thyroid Gland

The thyroid gland affects nutrition through its influence on absorption, on the basal metabolic rate, and on anabolic processes.

The rate of absorption of those substances which pass through the intestinal wall by other means than simple diffusion is dependent upon the presence of the thyroid hormone. Althausen (16) has shown that the absorption of sugars and fatty acids is delayed in myxedematous patients and in thyroidectomized rats. If thyroid hormone is administered in excess, the rate of absorption of these substances is increased above normal (Table 3). This increased rate of absorp-

tion of glucose in hyperthyroid subjects accounts for the high oral glucose tolerance curves which are often seen (17). Unless fasting blood sugars are above the normal level, such tolerances do not indicate diabetes but simply the increased rate of passage from the intestinal tract. The converse is true in myxedema. These patients often show a flat glucose tolerance curve when the carbohydrate is administered by mouth. Much more can be learned regarding glucose

TABLE 3. INTESTINAL ABSORPTION OF CARBOHYDRATES IN NORMAL, HYPERTHYROID AND THYROIDECTOMIZED RATS

Experimental condition	Substance administered	Amount absorbed in one hour per 100 gm. of weight, mg.
Normal	Dextrose	171±14*
Hyperthyroid	Dextrose	284±30
Thyroidectomized	Dextrose	91± 5
Normal	Galactose	187±27
Hyperthyroid	Galactose	273±18
Normal	Starch	126±24
Hyperthyroid	Starch	196±14

* Standard deviation.
(T. L. Althausen, *J.A.M.A.*, *115*: 101, 1940.)

utilization in patients with thyroid disturbance if intravenous tolerances are used.

The absorption of amino acids does not seem to be disturbed by changes in thyroid function (16). Disturbances of absorption cannot, therefore, account for failure of growth in hypothyroid individuals.

Aside from the effect on absorption, the thyroid gland does not seem specifically to affect carbohydrate metabolism as a whole. Russell (18) showed that in hypophysectomized animals the administration of thyroxin restored the reduced absorption in the gut, but did not change the distribution of absorbed carbohydrate from the pattern seen in untreated pituitary deficiency. In such animals any abnormalities in carbohydrate metabolism due to the treatment would be most easily noticed because the compensatory adjustments controlled by pituitary hormones are eliminated.

The most widely known effect of the thyroid hormone is its effect on the oxidative metabolism of the cells of the resting organism. Apparently the thyroid hormone increases the catabolic rate and the output of energy of practically every cell of the body. Its outward evidences are well known in the mental sluggishness and muscular slowness of the hypothyroid individual, together with the extreme nervousness and muscular over-activity of the hyperthyroid subject. Because of this effect less food is needed in hypothyroidism and more in hyperthyroidism. This is particularly true of the energy yielding foods, but it is also the case with proteins.

The interplay of appetite in the disturbances of the thyroid gland must be taken into consideration in the thyroid patient. It is rare to see a truly obese individual with hypothyroidism. The slower emptying of the intestinal tract, together with the decreased protein anabolism, leads to a reduction of hunger which in some cases may overcompensate for the reduced metabolism. On the other hand in severe hyperthyroidism the appetite, while voracious, is not stimulated to the point of energy balance so that ordinarily there is a tendency to catabolize body protein in addition to that in the food.

The thyroid hormone is of fundamental importance in protein synthesis. The thyroidectomized animal or the cretin child does not grow: it becomes pot bellied but it is rarely obese. Administration of pituitary growth hormone to thyroidectomized animals has less effect than in normal animals (19), (Figure 2). Evans and co-workers (20) have found that in hypophysectomized rats the administration of a combination of the growth hormone and thyrotrophic hormone is synergistic; the combined effect is greater than the sum of either alone. While the clear-cut evidence of the interrelationships of these two important factors in growth has only recently been worked out, clinical experience had long ago demonstrated the importance of thyroid function in growth even where the thyroid was not the primary deficiency involved.

While adequate thyroid hormone is necessary for growth in young animals, excess will cause *loss of weight* in adults. The failure to maintain weight often is due to a limitation in the intake of some essential factor. The increased catabolic processes involve increased wear and tear on the already existing structures and, therefore, the