

**NUTRITIONAL INTERRELATIONSHIPS OF THE THYROID
AND OTHER ENDOCRINE GLANDS**

A PROFESSIONAL PAPER

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BY

Arlene Beth Bouck, B.S.

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Approved by:

Head, Major Department

Adviser

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INTRODUCTION

As research findings broaden our knowledge of biological systems, it becomes apparent that the endocrine glands and their secretions are vitally important to and participate in almost every bodily function, including the utilization of nutrients. More information is needed to interpret the influence of these glands, especially at the human level. Endocrine glands may be defined as organs in the body which produce secretions that pass directly into the blood stream. Because these secretions are not carried from endocrine glands by means of ducts, they are sometimes referred to as ductless glands. About 1900 the view emerged that iodine is an essential component of a molecule synthesized by the thyroid gland (39). Starling (7) first used the term "hormone" (Greek *hormōn*, exciting, setting in motion) in 1905 to refer to his new discovery of the action of secretin. Isolation and structural determination of hormones has been the subject of much twentieth century research. Researchers are beginning to realize that neural and endocrine systems are integrated and are not separate entities as was formerly supposed. Hormones of the endocrine glands may act on the nervous system, and nerve impulses from the nervous system frequently stimulate or inhibit endocrine glands. Most biological phenomena are controlled by both the nervous system and the endocrine system.

Hormones released by endocrine glands appear to act upon tissues and organs through complex mechanisms which are not completely understood. The effectiveness of the hormones depends on several physiological states, such as the ability of the cells to respond to them, and the presence of

other substances in body fluids. It is known that endocrine hormones control certain physiological processes such as growth, reproduction, metabolic rates and blood chemistry. It is recognized that the central nervous system of animals and human beings contain nerve cells that can function as glands. These cells appear to secrete neurohormones at their terminals, which are believed to occur near blood vessels, and which are often located within glandular lobes such as the lobes of the thyroid. As relates to composition, chemistry and mode of action, neurohormones of the neurohypophysis are understood, but further isolation and identification of many are still needed. Neurosecretory cells link the nervous system and the endocrine system; they receive impulses from the central nervous system and respond to these impulses by releasing neurosecretions which stimulate or inhibit endocrine glands. Conversely, influences of endocrine glands upon the central nervous system are equally important.

It is interesting to scan the literature on endocrinology to discover how thought has changed and how thinking has advanced as a result of findings in this area. The first attempt at isolating the active principle of the thyroid was by Baumann in 1895 (39). Apparently this substance was not pure because it was noted that it sometimes was found to be completely void of activity. Baumann thought that it might be iodothyryn or iodo-thyro-globulin and proposed the term "thyryne". Substances which are now termed hormones were earlier called "autocoids". This term was used for substances that were formed by an organ and which were passed into circulation to produce effects on other organs. Schaffer (39) in 1913 noted that colloid was occasionally seen in the thyroid, and seemed to think that it might be an active thyroid

secretion containing iodine. This observation marked the beginning in the understanding of the close relationship between the size and structure of the thyroid and general nutrition. Schaffer (39) noted that hardly an organ remains unaffected by thyroid removal or atrophy.

It was stated in Recent Advances in Endocrinology in 1935 (7) that the most important change in concept concerning the thyroid gland was that it was thought to be interrelated with the parathyroid gland. It was also stated that "some secretion of the pituitary seems to control the thyroid and cause it to secrete". Extracts of this thyrotropic secretion were yet very crude. Unsolved problems relating to the thyroid at this time were: mechanisms by which thyroxine is formed, storage and secretion processes for thyroxine, and the chemical nature of thyroxine itself. It was thought that a relationship between the thyroid and gonads was possible, but this had not been investigated at that time.

The concept of interrelationships between nutrition and the endocrine glands is now generally accepted, and is the subject of this paper as it relates to one of the most important members of the endocrine system, the thyroid gland.

INTERRELATIONSHIPS OF THE THYROID GLAND AND OTHER ENDOCRINE GLANDS

The Parathyroid Glands

In human beings, the parathyroid glands are four bodies located on the lobes of the thyroid gland. Blood supply to the parathyroid glands is chiefly from the thyroid arteries. Although isolation of parathyroid extract was accomplished in 1924, the pure form has not yet been obtained.

Serum calcium regulation

Relationship of the endocrine glands to serum calcium dates back to 1909 when studies on the effect of parathyroidectomy on calcium levels began. It was demonstrated that this procedure in rats results in a rise in serum calcium (10). In 1925 Collip (9) restored calcium levels to normal by injecting dogs with parathyroid extract. Parathormone has now been isolated and purified, and it is fairly conclusive that the output of this hormone is stimulated by hypocalcemia and suppressed by hypercalcemia. This control is similar to that of a feedback mechanism. However, postulation of a feedback mechanism where stimulation of parathormone results in mobilization of calcium from bones and teeth into the blood stream in hypercalcemic states does not account for the stability in levels of blood calcium and has stimulated further research to determine precise mechanisms for control of serum calcium levels. From these studies evidence for the existence of calcitonin and thyrocalcitonin has evolved.

Thyrocalcitonin and calcitonin

Since 1961 experimental evidence has accumulated indicating that mammals have a fast acting hormone capable of lowering serum calcium. There is controversy at present as to whether this hormone originates in the thyroid gland, in the parathyroid gland, or in both glands. Copp et al. (10, 11) suggest the involvement of two parathyroid hormones -- parathormone and calcitonin -- released during hypocalcemia and hypercalcemia, respectively. Calcitonin has been found in plasma when high calcium levels are present. In sheep, the parathyroid is located on the thymus with a distinct and separate blood supply from the thyroid. This location aids in giving more conclusive results and by showing the presence of calcitonin in sheep parathyroid after calcium perfusion.

Gittes and Irvin (20) hypothesize that when a state of hypercalcemia exists, the parathyroid gland secretes a thyrocalcitonin releasing factor (TCRF), that affects the release of thyrocalcitonin, the thyroidal hormone which possesses serum calcium lowering activity. Removal of either the parathyroid or thyroid gland impairs the mechanisms which counteract hypercalcemia in rats; thyroidectomy has the greater effect of the two, producing impairment equivalent to that shown by removal of both glands. These effects are shown in Table I.

Hirsch et al. (27) confirmed the results of Gittes and Irvin by showing that thyroparathyroidectomy in rats results in higher serum calcium levels than does parathyroidectomy alone. Involvement of nerves between the thyroid and parathyroid and further depression of serum calcium levels after thyroid cautery was also shown. Cautery has a

significantly greater effect than does excision; immediate thyroidal cautery after parathyroidectomy by excision produces more significant results than parathyroidectomy alone. Further evidence for the presence of a calcium regulating factor in the thyroid comes from experiments which showed that parathyroid cautery and the excision of only a small amount of thyroid tissue does not alter serum calcium levels in rats.

Table I^a

RESPONSE OF THYROIDECTOMIZED AND PARATHYROIDECTOMIZED RATS TO HYPERCALCEMIA INDUCED BY INJECTIONS OF PARATHYROID HORMONE

Procedure	Calcium content of plasma before injection mg/100 ml	Calcium content of the plasma 6 hrs. after injection mg/100 ml
1. None	10.86	.32
2. Parathyroidectomy	11.23	1.45
3. Thyroidectomy	11.22	2.88
4. Thyroidectomy and parathyroidectomy	11.14	2.79

a. Taken from reference 20.

Interdependence with specific
physiological states and/or
nutrients

Vitamins C and D. Vitamins C and D are involved in calcium metabolism. Constant blood calcium concentrations are maintained by parathyroid hormone; when calcium blood levels are low, parathyroid hormone stimulates mobilization of calcium from the bones; when calcium blood levels are high, calcium is excreted by the kidney. Vitamin D is essential

for absorption of calcium from the intestine and for deposition of calcium in the bones. Because calcium salts are more soluble in acid, vitamin C enhances calcium absorption. There has been considerable controversy regarding the number of hormones secreted by the parathyroid glands.

Nerve trauma. Respiratory difficulties observed in most cases of nerve trauma suggest an effect on serum calcium levels, but mechanisms by which this occurs are unknown. Release of the thyroidal hypocalcemic factor during cautery could explain the greater effect of this procedure.

Tenenhouse et al. (47) have isolated thyrocalcitonin, showing it to be a polypeptide with molecular weight of 8700. Thyrocalcitonin does not seem to alter renal or gastro-intestinal calcium transport or to enhance calcium uptake by skeletal tissue. Thyroid extracts from hogs, deer, lambs, and human beings were tested in rats; all extracts except those of human origin had hypocalcemic activity. The specificity of this effect of the thyroid was demonstrated by administering extracts from kidney, lung, brain, spleen, liver and pancreas with no resultant lowering of calcium levels. Chausmer et al. (8) note that skeletal metabolism in dogs and human beings is slower than it is in rats and inhibition of bone resorption might not result in a comparable hypocalcemic response. They speculate that man may have lost the thyrocalcitonin factor due to a slower rate of skeletal metabolism and lessened ability to respond to this factor. Thyrocalcitonin activity has been demonstrated in monkeys; these animals have rates of calcium metabolism similar to that in man. It is the opinion of the present writer that

repeated efforts should be made to demonstrate thyrocalcitonin activity in man. Reports of Hirsch et al. (28) conclude that there is no evidence for secretion of calcitonin or thyrocalcitonin from the parathyroid gland. Rather, they think that their results substantiate the secretion of a hypocalcemic substance from the thyroid gland, thyrocalcitonin. Mihaud et al. (33) reported the thyrocalcitonin activity in extracts from six human thyroid glands when injected into rats and monkeys. Extracts of 2 or more grams were required to produce significant lowering of calcium levels; only 0.2 grams had been utilized previously.

Thyrocalcitonin antibody

Evidence for the presence of thyrocalcitonin antibody was obtained from the response of rabbits that were injected with thyrocalcitonin. Sera from these animals reached an antibody level high enough to react with thyrocalcitonin during the anamnestic response which was induced ten months after the primary immunization (10). A precipitate forms when thyrocalcitonin is incubated with its antisera, anti-thyrocalcitonin, the precipitate thus formed shows hypocalcemic activity which the supernatant does not have. This factor in immunized rabbit serum was shown to have the same heat stability as that of rabbit antibody, 60°C for 20 minutes.

The Pituitary Gland

The pituitary gland is a small body weighing about 0.5 gm. located at the base of the brain. This gland is composed of three lobes: an anterior lobe, an intermediate lobe and a posterior lobe. Secretions of the anterior lobe of the pituitary gland are (a) growth hormone, which

stimulates growth, (b) gonadotropic hormone, which stimulates the sex glands, (c) adrenotropic hormone, which stimulates the adrenal glands, and (d) thyrotropic hormone, which stimulates the thyroid gland.

Functions of the anterior lobe of the pituitary gland are interrelated with those of several other endocrine glands, including the thyroid gland. With development of better assay methods in the past five years, progress has been made in detecting thyrotropic stimulating hormone (TSH) in animal serum. However, there is still difficulty in detecting the minute quantities of TSH present in human serum, with present methods. Detection of TSH in animal serum has led to further elucidation of interrelationships between the thyroid gland and the pituitary gland. The pituitary secretion of TSH can be altered by the level of thyroid hormone in the blood, but it is uncertain whether thyroid hormones do this by acting directly upon the pituitary gland or whether this is an effect mediated through the hypothalamus. A further complication in research on thyroidal-pituitary interrelationships has been because of species differences in pituitary TSH (49) activity.

Growth hormone

Investigations of the influence of pituitary growth hormone and thyroxine at the cellular levels show that both of these hormones affect intestinal mitotic activity. LeBlond and Carriere (29) showed that total mitotic activity was lower after thyroidectomy, hypophysectomy, or both; depression in activity being of the magnitude of five and three per cent, respectively. Growth hormone alone increases mitosis to normal rates in all three types of surgery. Effects of thyroxine are

pituitary dependent since thyroxine restores mitosis to normal rates only in the presence of the pituitary. There is evidence that thyroidectomy interrupts secretion of growth hormone, indicating that this secretion is induced by the thyroid. Growth hormone and thyroxine seem to interact to increase the growth of intestinal tissues, which predominantly takes place by mitosis. Decreased mitosis could result from the depletion of glycogen reserves, which may be produced by thyroxine administration alone. The overall affect of thyroxine may depend on the balance between its indirect tendency to cause increased secretion of growth hormone and a direct tendency to decrease the rate of mitosis.

Hypophysectomy

Hypophysectomized animals treated with thyroxine showed retarded growth and lack of weight gain, as compared to normal animals (17). However, organ weights were higher in hypophysectomized animals treated with thyroxine than in non-treated animals, although these weights were still below values for intact animals. Atrophy of endocrine glands caused by hypophysectomy is not altered by thyroxine. Growth ceases immediately after hypophysectomy, while thyroidectomized animals continue to grow for approximately ten days. In both of these animal groups thyroxine increases the heart rate and oxygen consumption to values considered to be normal. These three effects are results of the stimulatory effect of thyroxine on metabolic activity. The administration of thyroxine results in normal weight increases only when the pituitary is intact. Results of studies indicate that the secretion of growth, gonadotropic, and corticotropic hormones by the pituitary

does not take place in the absence of the thyroid. However, sufficiently high levels of thyroxine inhibit thyrotropic secretion by the pituitary. Thyroxine appears to control a number of pituitary secretions since it causes: the reduction of thyrotropic secretion and the increase of gonadotropic, corticotropic, and growth hormone secretions. Functional hypertrophy due to increased metabolism or increased release of growth hormone may explain the effect on organ weights. Eartly and LeBlond (17) refer to unpublished work by Carriere which showed that the decreased diameter of kidney tubules was only partially restored by thyroxine. Simpson et al. (42) showed restoration of total body weight by injections of growth hormone alone, whereas proportionate organ weights were not restored without administration of both thyroxine and growth hormone. Data from this experiment are shown in Table II.

It appears that the thyroid gland has a (a) direct effect on glucose metabolism, (b) a hypophysis-mediated effect on body growth, the adrenals and the sex glands, and (c) a combination of direct and hypophysis-mediated effects on the size of non-endocrine organs. Table III shows these relationships.

Gastric secretion

Possible interaction of the thyroid gland on gastric secretion and the essentiality of pituitary and adrenal hormones has been investigated. Nasset et al. (35) found that injection of whole thyroid, thyroxine, triiodothyronine, and iodinated casein reduced gastric secretion in intact and thyroidectomized dogs. It was suggested that elevated tissue concentrations of thyroid hormones reduce the ability of gastric

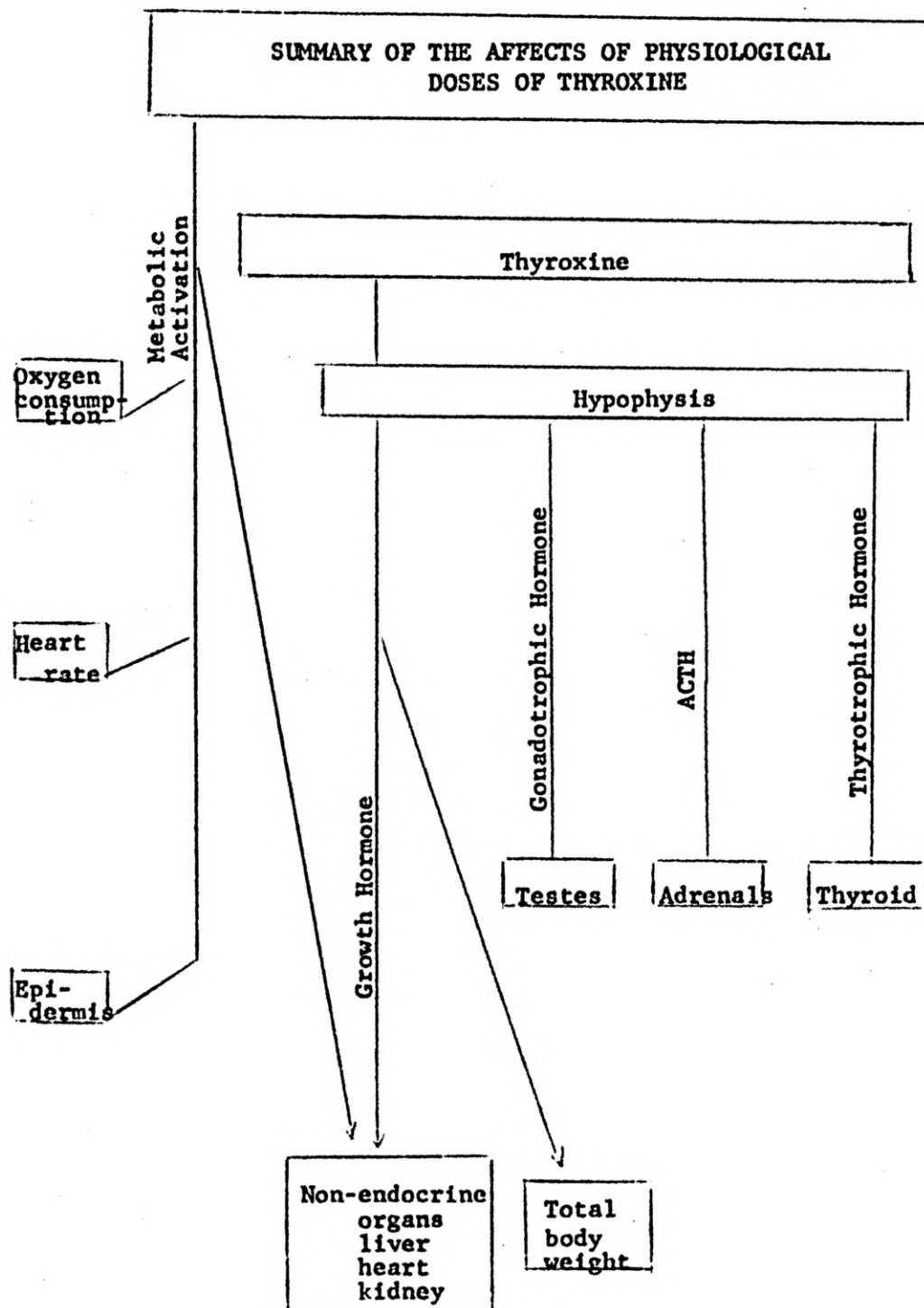
Table II^a

INFLUENCE OF THYROXINE ON ORGAN WEIGHTS OF 10
HYPOPHYSECTOMIZED RATS FOR 19 DAYS.
RELATIVE WEIGHTS ARE GIVEN IN MG/100 GM. BODY WEIGHT.

<u>Hypophysectomized</u>	<u>Thyroxine injected Hypophysectomized</u>	<u>Intact Control</u>
867	1095	1690
388	486	672
201	313	367
649	728	1052
5120	5725	8594
269	363	500
12	12	30
577	497	2615
51	43	445
12	12	23

^a. Taken from reference 42.

Table III



mucosa to mobilize energy. Thyroid hormone injections on gastric secretion in the frog, dog, rat, guinea pig and rabbit result in reductions in secretion levels. Although the exact mechanism for this has not been elucidated, interaction of the adrenals, pituitary and thyroid is suggested.

Thyrotropic secretion

The relationship of hypophysial thyrotropic secretion to the level of thyroid hormone in the organism has been studied. Alsheim (1) noted a 50 per cent increase in thyrotropic content of the pituitary in rabbits 60 days after thyroidectomy. If these same rabbits are subjected to extirpation of sympathetic nerves involved with pituitary impulsation, thyrotropic hormone in the pituitary drops below normal. Withdrawal of thyroid hormone seems to have a stimulating effect on the pituitary secretion, which is exerted by sympathetic nerve impulses.

Interrelationships of the pituitary and thyroid have been recognized since the nineteenth century, and knowledge of this has progressed from the discovery of the factors which are interrelated to the present concentration on mechanisms and sites of reaction. Research in this area presently centers around the neural-humoral considerations of interrelationships between the two glands.

The Adrenal and Sex Glands

The adrenal glands are composed of two small lobes lying above the kidneys. Each lobe weighs only approximately 5 grams, but the blood supply, in proportion to weight, is greater than that of other body organs. Each adrenal lobe is composed of two distinct layers which

differ in function: the cortex and the medulla. Cells of the medulla secrete adrenaline, which affects blood pressure, pulse rate and glycogenolysis. Aldosterone, which affects metabolism of electrolytes and water, is secreted by the cortex. Experiments with animals have demonstrated that the cortex is essential for life; however, demedullated animals survive.

Thyroid-adrenal interdependence

Studies of the specific effects of thyroid on the adrenals in the rat show that administration of thyroid results in the enlargement of the adrenal cortex. Wallace et al. (50) showed that in the earlier stages of hyperthyroidism the adrenals appear to be discharging increased amounts of cortical hormones into the blood stream. The level of thyroidal stimulation determines size and secretory activity of the adrenal cortex; doses within the physiological range appear to have no effect. The initial response of the adrenals to thyroid stimulation appears to be a decrease in ascorbic acid content and in the size of the adrenals, until a balance between demand and synthesis of ACTH has occurred.

Sodium balance has been studied and shown to be an adrenal-thyroid regulated mechanism. Reduced rates of glomerular filtration and renal sensitivity to antidiuretic hormone and to aldosterone are noted in hypothyroidism in rats (46). It is not known whether decreased renal sensitivity is a specific or nonspecific manifestation of reduced metabolic activity. Kidneys of rats given propylthiouracil (PTU) are

capable of responding to aldosterone but the threshold for response is elevated almost nine times. Hypothyroid rats are unable to maintain sodium balance when sodium is restricted but euthyroid rats maintain sodium balance on the same diet; hypothyroid rats also excrete more sodium and potassium than controls. Hypothyroidism may interfere with secretion of aldosterone by the adrenal cortex. Patterns of sodium intake similar to those observed in hypothyroidism have been observed in adrenalectomized rats. Impaired renal responsiveness to aldosterone appears to be an important factor in decreased tubular reabsorption. The mechanism by which thyroxine promotes renal responsiveness to sodium retention has not been elucidated, but it is known that sodium reabsorption is an energy requiring process involving cells lining renal tubules. The effect may be one of interaction of thyroxine and aldosterone, which functions in the regulation of energy metabolism. Thyroxine has been reported to increase sodium transport in toad skin and bladder; this response is accompanied by an increase in oxygen consumption by these tissues.

Antithyroid drugs

Fregly et al. (19) showed that administration of antithyroid drugs to rats (a) increases the spontaneous intake of sodium above levels for controls, (b) prevents aversion to sodium chloride that is characteristic of renal hypertension, and (c) results in negative sodium balance in sodium and potassium deficient diets. The negative sodium balance occurs as a result of greater loss of sodium in the urine and inability to retain sodium. Thyroxine administration was shown to correct these

conditions. Decreased renal production of renin and decreased production of aldosterone were present in hypothyroid animals.

The mammary gland

Nursing or some events associated with nursing seems to provide a stimulus for more active thyroidal secretion. Variations in the amount of milk synthesized by and removed from the mammary gland seem to cause variations in blood iodine levels. Because thyroxine has a high iodine content, this increase is indicative of a stimulus to thyroidal secretion. Grosvenor (22) hypothesizes that removal of milk from mammary glands activates metabolic processes associated with milk production, causing increased need for thyroidal hormones. Because thyroidal hormones influence several enzyme systems, they may be metabolized to a greater degree in metabolically active tissues resulting in lowered blood levels of iodine and increased thyrotropin secretion. The mammary gland of a lactating rat secretes a large amount of iodide which binds to milk protein. It is also possible that interceptors within the mammary gland activate the hypothalamus by means of sympathetic nerves causing release of thyrotropin. Most data suggest that removal or reaccumulation of milk, rather than excitation of nerves in the skin or nipples, causes the stimulus to thyroid secretion. The effect seems to be mediated by the pituitary. It is known that thyroid hormones influence the intensity of milk secretion. In lactating rats, higher thyroid activity is correlated with greater milk yield.

Maternal and fetal thyroid glands

Florsheim and El Kabir (18) showed an interrelationship between the weight of fetal thyroid and maternal thyroid. Fetal body weight and the weight of fetal thyroid decreased when pregnant rats were fed goitrogenic drugs. Maternal and fetal body weight and thyroid weight decreased proportionately. The yet uninvestigated possibility of a transplacental effect of TSH was also discussed by these authors.

Electrical stimulation of the hypothalamus

Studies relating to the effect of the hypothalamus on other endocrine glands began in 1920 when investigators showed that damage to the hypothalamus leads to genital atrophy in dogs, even when the hypophysis is intact. Evidence that the hypothalamus controls the autonomic nervous system and affects responses of the gonads has been accumulating since that time. Ovulation and increased thyroidal activity results in rabbits from stimulation of anterior or middle regions of the hypothalamus, while stimulation of the posterior regions of the hypothalamus does not produce these effects. Evidence from investigations using different species indicates that secretion of pituitary gonadotropins, corticotropin, and thyrotropin may be affected by the hypothalamus (14). The implication of these studies is that nervous impulses discharged in hypothalamic centers result in release of hormones from the pituitary, which may affect the adrenal glands, the gonads and the thyroid gland.

It has been known since 1937 that electrical stimulation of the hypothalamus evokes secretion of adrenaline and that adrenaline may inhibit thyroid activity by a vasoconstricting action on the gland.

Studies with rabbits have shown that doses of adrenal steroids necessary to produce thyroid inhibition are within physiological range. Adrenal steroids may affect thyroid activity by suppressing the secretion of TSH from the pituitary. A rise in the level of thyroid hormone may also stimulate the pituitary adrenal axis. According to results obtained by Harris and Woods (25), stimulation of more posterior parts of the hypothalamus seem to excite ACTH release while those of the anterior excite TSH release. Evidence supports the "median eminence" as the zone where neural mechanisms for ACTH and TSH release overlap. Activation of this region of the hypothalamus may raise blood levels of adrenal steroids resulting in a secondary effect of inhibition of TSH release.

Electrical stimulation of the hypothalamus has been shown to reduce pituitary content of thyrotropin (TSH) and to increase plasma TSH concentration, resulting in stimulation of the thyroid. Effects of hypothalamic stimulation on the thyroid were mediated through the anterior pituitary, the site of neural structures which affects TSH secretion. Portions of the hypothalamus which regulate TSH and ACTH secretion appear to overlap; electrical stimulation of these sites has effects on both the thyroid gland and adrenal glands. Earlier studies postulating extrahypothalamic interplay between the thyroid and the adrenals are not substantiated by recent work (14). Decreased blood concentration of thyroid hormone seems to be mediated by the hypothalamus. The hypothalamus appears to reflect changes in thyroid activity neurally and to maintain thyroid activity under conditions of changing environment. Confirmation of the increased

release of adrenal corticoids and TSH (25) through stimulation of the anterior pituitary was accomplished by Harris and Woods. Evidence for this hypothalamicthyroidal effect was as follows: (a) hypothalamic stimulation excites the transplanted thyroid as well as the normal thyroid by means of a humoral effect and (b) doses of TSH simulate the effect of hypothalamic stimulation. Results also showed that electrical stimulation of the anterior pituitary gland, which does not spread to hypothalamic centers, does not evoke release of gonadotropic hormone.

THE THYROID GLAND AND ENERGY METABOLISM

Literature pertaining to the thyroid gland presents evidence for the effect of thyroid hormone on energy metabolism. These include, in addition to its role in the basic mechanisms involved in the iodination of thyroid hormone, and in the release of thyrotropic stimulating hormone, biological oxidations, respiration in intestinal mucosa and glucose utilization. The effects on glucose utilization appear to be (a) decreased glycogen content in the liver, (b) increased levels of glucose in the blood, (c) and increased oxidation of glucose in cells.

Glucose Utilization

Levin et al. (30) utilized two methods of inducing the hyperthyroid state in rats, oral and injection; rats rendered hyperthyroid by oral means developed more severe states. Significantly higher intestinal weights per kg. body weight were observed in hyperthyroid animals. Rats were rendered hypothyroid by feeding with thiouracil and subsequent thyroidectomy. Glucose transfer in hypothyroid rat intestinal mucosa was similar to that in normal animals suggesting that the effect of the thyroid on carbohydrate utilization is metabolic rather than on the intestinal transport processes. To substantiate this, Levin et al. (39) again found increased rates of glucose metabolism in hyperthyroid animals. Investigations of specific sacs of rat intestine showed the greatest increase in glucose metabolism in sac five, with only minor increases in other sacs. Hypothyroid

animals showed little difference in glucose metabolism from controls. Increased intestinal weights per kg. body weight in hyperthyroidism were noted. Only slight increases in glucose were noted in sac five. The question in the mind of researchers was whether this increase in metabolism was due to increased intestinal weight, increased metabolic activity of individual cells or to increased total numbers of intestinal cells. Results did not show increases in intestinal fluid transfer, even though increased glucose metabolism would supply energy for this. Levin et al. (39) noted the possibility that thyroxine may stimulate glucose metabolism by reducing the efficiency of tissues in utilizing energy for biological work, and point to evidence of Nasset and Goldsmith (35) which showed that hyperthyroidism impairs the ability of gastric mucosa to mobilize energy. Halliday et al. (24) suggest that hyperthyroidism inhibits the intestinal mechanism for glucose transfer, but that this inhibition is offset by physiological adjustments such as increased gastro-intestinal motility. Specific effects of iodide on glucose metabolism and the regulation of iodination have been studied. Using sheep thyroid incubated in glucose media, Green (21) showed that the addition of iodide stimulates oxygen consumption and glucose oxidation. These effects seemed to be results of increased Krebs cycle oxidations.

Biological Oxidations

Attempts are being made to investigate the effect of thyroid hormone on oxidation and mitotic activity. Thyroidal control of terminal oxidation by regulating the efficiency of energy conservation

and by inducing mitochondrial swelling is not substantiated by the work of Bronk et al. (4) who showed that the thyroid gland affects the total capacity of the electron transport system without affecting phosphorylation. Results showed that thyroxine stimulates electron transport in mitochondria from thyroidectomized rats. Thyroidal hormone was shown to stimulate oxidation, probably due to increased synthesis of electron transport components or enzymes. The rate of oxidation of substrates with NAD (nicotinic acid adenine dinucleotide) dehydrogenases was affected to a greater degree when substrates were combined than when they were tested individually. Because of the unaltered rate of oxidation of slowly oxidized substrates, it was concluded that the overall rate of the citric acid cycle is not affected. Neither normal nor T₃ treated mitochondria showed increases in oxidation rates in vitro. Thyroid hormone is capable of affecting terminal mitochondrial oxidative capacity without affecting individual dehydrogenases. Effects of triiodothyronine were similar to, but more potent than, those of thyroxine. Direct activation of oxidation processes by thyroid hormones reported in this and other work, refutes previous suggestions that changes in oxidative capacity reflect adaptation to increased demands for energy. Increased demands for energy as a result of increased activity have been shown to stimulate the activity of the citric acid cycle without affecting electron transport capacity; triiodothyronine has the opposite effect. Increased activity caused by triiodothyronine seems due to direct activation of the electron transport system which is a prelude

to other energy requiring processes.

Respiration in Intestinal Mucosa

Bronk et al. (5) measured galactose and xylose accumulation in the intestinal mucosa of normal and thyroidectomized rats. Findings indicated that thyroidectomy does not alter accumulation or penetration of sugars or respiration rates in intestinal mucosa. However, treatment of thyroidectomized animals with T_3 increased respiration rates in the jejunum above that of non-treated thyroidectomized animals and controls. Thyroidectomy at 25 days of age produced no marked effect on the length of the small intestine, but total dry weight, fat-free dry weight and fluid content are reduced; thyroidectomy appears to reduce solid and fluid content of the jejunum, as shown in Table IV. Although results show no impairment of basic sugar transport

Table IV^a

GALACTOSE ACCUMULATION: JEJUNAL FLUID, AND JEJUNAL DRY WEIGHT
IN RAT INTESTINE.

Animals	Galactose accumulation in mucosal tissue mg/g fat free dry weight of tissue (FFDW)	Jejunal tissue fluid mg/cm	Jejunal dry weight mg/cm
Thyroidectomized	14.51	42.4	11.9
Thyroidectomized and injected with T_3	18.6		
Age controls	13.88		
Weight controls	12.14		
Age and weight controls		63.6	14.5

a. Taken from reference 5.

processes or decrease in the rate of oxygen consumption, a depression of total absorptive capacity and of total oxygen consumption in the intestine in thyroidectomy are indicated. Bronk et al. (5) refer to findings of Althausen in 1949 which showed decreased sugar absorption in vivo in thyroidectomy. When animals were subjected to thyroidectomy 7-8 weeks before experimentation began, findings showed no impairment in sugar absorption after a lapse of time. This lack of response does not show that the thyroid has no affect on these processes because thyroidectomy may cause compensatory effects in another organ.

Iodination of Thyroid Hormone

In the rat and in man, increased plasma concentrations of iodide are associated with the increased thyroïdal uptake of iodine. Increased uptake occurs until optimum iodide concentration is reached. Total iodinations in sheep thyroid slices have been shown to increase as iodine concentration increases. It seems that oxidation of iodide increases the rate of oxidation of other substrates. Loss of stimulation at higher concentrations may be related to inhibition of thyroid hormone formation. Schussler et al. (40) present evidence that synthesis of thyroïdal hormone proceeds in the following steps: (a) concentration of iodide from extracellular fluid, (b) oxidation accompanied by organic binding of iodine to yield iodotyrosines, and (c) coupling of iodotyrosines to yield iodothyronines. The last two reactions seem to occur within the thyroglobulin molecule. These reactions are further evidence that TPNH serves as a H^+ donor for peroxide formation, that rates of iodination are regulated by TPN linked

dehydrogenations, and that the hexose monophosphate shunt is the source of reduced TPN. Glutathione, which is present in many tissues, including the thyroid, has been shown to inhibit iodination; the mechanism for this inhibition is not known. Glutathione may act as a competitive substrate for an oxidant of iodide. It is hypothesized that TPNH probably serves as an intermediate in generating an agent capable of oxidizing iodide. Schussler et al. (40) showed that TPN, the cofactor for hexose monophosphate shunt oxidations, is a potent stimulus for thyroid iodinations. They postulate that TPNH serves as a hydrogen donor for peroxide formation. Current concepts of thyroidal iodine metabolism hypothesize formation of hydrogen peroxide for peroxidations and the presence of peroxidase for catalysis in iodine metabolism. Glycolysis and the hexose monophosphate shunt which appear to be activated by iodide may provide oxidants which in turn act on iodide. Excess iodide appears to inhibit glucose metabolism, Krebs cycle, and mobilization of substrate. Glucose uptake was not significantly affected by changes in iodide concentration.

Work with euthyroid human beings by Mercer et al. (32) indicates that administration of iodide reduces thyroxine secretion and that this effect lasts throughout the total period of iodine administration; showing that the pituitary does not respond to this reduction by additional secretion of thyrotropin. This work gives support to the belief that iodide affects the pituitary as well as the thyroid gland.

Release of Thyrotropic Stimulating Hormone

It is generally believed that the central nervous system can modify thyroid function by adjusting the release of thyrotropic stimulating hormone (TSH) by the pituitary. It is known that the hypothalamus is the center of neural mechanisms that regulate TSH release. Redding et al. (37) cite evidence for purification of hypothalamic peptides which increase the release of TSH in vivo and in vitro. Large doses of thyroxine were shown to inactivate the effect of TRF. Redding et al. (37) also showed that both TSH concentration in the pituitary and thyroid activity in rats are reduced by administration of morphine. They hypothesized that the effect was mediated through hypothalamic centers rather than by direct action on the pituitary; and that a hypothalamus-pituitary-thyroid interrelationship is involved. Analysis of the amino acid content of thyrotropic releasing factor (TRF) showed lysine, histidine, arginine, threonine, alanine, aspartic acid, leucine, tyrosine, phenylalanine, valine, serine, proline, glutamic acid and glycine to be present. The structure of TRF has not been completely elucidated.

THE THYROID GLAND AND PROTEIN METABOLISM

Evidence for an effect of thyroid hormone on protein metabolism comes from the following observations of hypothyroid states: (a) subnormal growth of animals and human beings, (b) decreased protein content of rat carcass, liver and kidneys and (c) deposition of mucoprotein in tissues of human beings. From these investigations further research has evolved.

Protein Synthesis

Thyroxine has been shown to enhance amino acid incorporation into microsomal protein in rat liver in vitro (38). In the literature, there are some reports that thyroxine has no effect on RNA polymerase activity, in vitro, and others that it increases RNA-polymerase activity in vivo. Roodyn et al. (38) report that triiodothyronine injection doubles the amino acid incorporation into protein in thyroidectomized rats, but causes only slight increases in controls. Studies have indicated that thyroxine has a stimulatory role in the last step of the reactions which have been shown to be the mechanism of protein synthesis (14). This step involves the transfer of soluble-RNA to microsomal protein. The currently accepted theory of protein synthesis is shown below:

amino acid
activating enzyme

- 1) Amino acid + ATP $\rightleftharpoons$ Amino acid enzyme + P Pi
- 2) Amino acid - AMP - enzyme + S-RNA $\rightleftharpoons$ S-RNA-AA + AMP + enzyme
- 3) S-RNA-AA + microsomes $\xrightarrow{\text{GTP}}$ Protein - AA + RNA

Although the possibility that thyroxine is involved in activating amino acids cannot be entirely excluded, evidence suggests that its effect is limited to the final step, as suggested by the deleterious effect of diluting soluble-RNA bound valine. It does not appear that the effect of thyroxine is on GTP, because GTP causes a small increase by itself, but does not replace the effect of thyroxine. Investigations of the possibility that thyroxine enhances amino acid incorporation into protein by activating ATP regeneration of GTP gave negative results. In addition, cofactors cannot replace the effects of thyroxine. Mitochondria and oxidizable substrate are required for the effect; mitochondria probably provide ATP for GTP regeneration.

Studies by Tata et al. (45) showed that triiodothyronine increases amino acid incorporation into protein and that the stimulation is that of rate of protein synthesis. They observed equivalent stimulation of both mitochondrial and microsomal protein synthesis, but noted greater total activity in the microsomal system. These researchers feel that the primary effect of thyroid hormones is on the nuclear mechanisms that regulate synthesis of cytoplasmic protein. Stimulation of mitochondria by thyroid hormones results in increased rates of oxidation of substrates; it is not known whether this is the cause or effect of changes in mitochondrial protein synthesis. Bronk et al. (4) suggest that thyroid hormone diverts high energy intermediates into amino acid activation processes.

Proteolysis

The presence of acid phosphatase in thyroid epithelium was first

demonstrated by Balasubramaniam (2) but details for the locations or mechanisms of sites of action were not given. By 1948, the presence of non-specific esterases in the thyroid was fairly well established (2).

In vitro studies (2) in which thyroidal proteinase and peptidase were incubated with thyroglobulin which was labelled in vivo, showed the optimum pH ranges for these enzymes to be 3 to 5 and 4 to 5.3, respectively. ATPase was shown to be catalytic for the release of either iodotyrosines or thyroxine from thyroglobulin; whereas peptidase had almost no effect on intact thyroglobulin. Specific enzymatic contributions and determinations were not made. McQuillan et al. (31) demonstrated that iodinated tyrosines and thyronines could be liberated by partially purified thyroid proteinase from pig thyroid. Two peptidases, cysteinyl tyrosinase and N-acetyl-L-phenylalanyl-L-tyrosine, were also isolated. Further research showed that thyroid hormone is chemically bonded by means of peptide linkages within thyroglobulin. Recent evidence (27) indicates that TSH enhances the proteolysis of thyroglobulin within thyroid cells, causing release of thyroid hormones.

Colloid Droplets

Although TSH does not increase cathepsin synthesis in vitro it is possible that it may do so in vivo. The presence of colloid droplets in the cytoplasm of rat thyroid epithelial cells after TSH stimulation has been demonstrated by Wollman (51). Esterase and acid phosphatase activity has been found in droplets and granules in thyroidal epithelial cells in increased concentrations after TSH injection. Hypophysectomized, TSH injected rats had formation of colloid droplets in epithelial cells 10

minutes after injection, and migration of esterase and acid phosphatase from the basal to the apical end of the cell is noted in 15 to 30 minutes. Results indicated that intracellular colloid droplets are derived from the lumen of the follicle. The mechanism for colloid formation into droplets is not conclusive, but evidence for pinocytosis exists.

Lysosomes

It is felt that lysosomes are the source of the proteolytic enzymes and that enzymatic contribution takes place by the fusion of droplets and lysosomes, or by inclusion of the enzymes at the time of droplet formation. It was also shown that lysosomal cathepsin cleaved thyroglobulin in pH 3.6, resulting in release of iodothyronines. One of the difficulties involved in accounting for thyroxine release from thyroglobulin has been finding proteolytic enzymes with the pH optimum around that of body fluids. It is now suggested that the combination of cathepsin and thyroglobulin within intracellular organelles produces a pH between 4.5 and 6.0 which is near to, or within the lower limits of the physiological range.

Previous work (48) showed that lysosomes contain esterase and acid phosphatase, causing investigators to consider the possibility that lysosomes are present in the thyroid gland. It has been shown that newly formed colloid droplets do not contain enzymes, but "enzyme containing" droplets (lysosomes) have been viewed microscopically in close proximity to "enzyme free" droplets after TSH injection, indicating enzymatic

transferral into the colloid droplets. TSH may cause the shift to optimum pH. By observations with the electron microscope it is possible to see dense membranes of acid phosphate granules in the process of fusing with droplet membranes.

Balasubramaniam et al. (2) showed that the proteolysis of thyroglobulin occurred at pH 3.5, and that the presence of acid hydrolases in lysosomes, including cathepsin, had an optimum pH of 3.6. The presence of lysosomes in the thyroid has been demonstrated by Nadler and LeBlond (34). As lysosomes are unstable at a pH below 5, investigators think that release of thyroxine must occur at a pH higher than 5. The possibility that hormones facilitate penetration of the substrate into the lysosome rather than initiating enzymatic release, is suggested by Van Lancker (48). The concept regarding lysosomes has progressed into theories in many areas since they were first observed by use of the electron microscope in 1956.

From the preceding discussions, it can be seen that the mechanism for the stimulation of protein metabolism by thyroid hormone is still obscure and in the theoretical stage. Questions as: does thyroxine release a substance which alters mitochondrial permeability, is the effect on the transfer step one of acceleration of intermediate steps, or of alteration of microsomal permeability remain to be answered.

SUMMARY

Scientific progress in the study of nutritional interrelationships of the thyroid and other endocrine glands has resulted from improved methods, tools and techniques of research: (a) the electron microscope for visualization of cellular processes, (b) isolation of components of tissues cultures, (c) perfusion of whole organs, and (d) radioactive isotopes for investigation of intermediary metabolism. Although progress has been made, there is need to focus attention on remaining problems. The mechanisms by which hormones are released remain unsolved. Further study reveals that many hormones and nutrients form overlapping systems and rarely act in isolation. Determination of hormonal balance and interaction is important to the further elucidation of nutritional and endocrine interrelationships. The endocrine system is considerably more complex than was formerly thought. Another perplexing problem is inherent in the continuing discovery that the action of nutrients and hormones may be modified by other substances present in glands or body fluids. New synergisms are continually being discovered and investigated. When nutrients or hormones are administered with other compounds or in varying concentrations, they may cause effects that are far different from those caused by the single hormone or nutrient. There is not sufficient information to disclose how hormones and nutrients perform at the cellular level in vivo. In addition, evidence shows that both hormones and nutrients may modify enzymatic reactions within cells. However, the enzyme systems upon which they act are not completely understood. Evidence that the same hormone or nutrient is involved in multiple mechanisms, depending on the site

of action, is being uncovered; and this further complicates the problem. Studies on nutrient and hormone interrelationships usually are performed with experimental animals. Relationships discovered in animals frequently do not apply equally, if at all, to human beings.

Although many problems, of course, remain unsolved, there will no doubt be continued progress in the study of the interrelationships of nutrition, the thyroid and other endocrine glands.

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