Nutrition and Diseases of the Endocrine Glands

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DISEASES OF THE ENDOCRINE GLANDS illustrate the importance of hormonal and nutritional factors in the regulation of metabolism in humans. Hormones influence the rate and direction of metabolic processes. Therefore, a decreased or increased secretion of any hormone may alter the total carbohydrate, protein, fat, mineral, or vitamin requirements.

DISORDERS OF THE PITUITARY GLAND

The ability of man to adapt to a constantly changing environment is made possible by the integrated actions of the nervous and endocrine systems. The main site of this integration is through a hypothalamus-pituitary communication, and the nervous system influences the rate of secretion of the various hormones. This is accomplished by hypothalamic "tropin-releasing factors," which are carried to the pituitary by a portal circulation. These factors regulate the rate at which tropic hormones such as thyrotropin, corticotropin, or the gonadotropins, are released.

The neurohypophysis and hypophysis, with direct secretomotor nerve connections between them, secrete antidiuretic hormone, oxytocin, and tropin-releasing factors. The adenohypophysis secretes growth hormone, corticotropin, thyrotropic hormone, follicle-stimulating hormone, luteinizing hormone, prolactin, and melanocyte-stimulating hormone. Thus, disorders of the pituitary gland are reflected by the nature and extent of the involvement of its various hormones. Nutritional effects, likewise, depend upon the type of abnormality that exists in the pituitary or hypothalamus.

Acromegaly

Excessive secretion of growth hormone, usually due to an eosinophilic adenoma, produces gigantism prior to fusion of the epiphyses or acromegaly in the adult. Growth hormone causes growth in almost all tissues, although skeletal maturation and sexual development are not significantly affected (1).

There is no difficulty in the absorption or utilization of food in the acromegalic patient. Although an increased metabolic rate with normal thyroid function exists, the anabolic effects of growth hormone predominate when adequate nutrition is provided.

Growth hormone has important effects on protein metabolism. It favors the formation of lean body protein in contrast to another anabolic hormone, insulin, which increases body fat as well as protein. Excessive secretion of growth hormone decreases blood and urine urea. Amino acid incorporation into protein is accentuated resulting in a positive nitrogen balance.

The anabolic effects of growth hormone are not universal for all tissues. Protein anabolism is made possible to a large extent from the energy provided by adipose
tissue. Increased lipolysis occurs from depot fat with resultant increases in plasma free fatty acids. Liver triglycerides increase and elevations of alpha and beta lipoproteins have been noted. Ketogenesis and accelerated fat oxidation can be recognized by a lowering of the respiratory quotient (2). The selective utilization of fat for energy is a valuable effect for a hormone to have if the sparing of protein is its ultimate purpose. One of the more important actions of growth hormone is its ability to mobilize fatty acids from fat stores early in the fasting state and during exercise.

The increased prevalence of diabetes mellitus in acromegalic patients suggests an important relationship between growth hormone and carbohydrate metabolism. Young (3) found that injection of anterior pituitary extracts could produce permanent diabetes in animals. The injection of growth hormone into hypophysectomized animals produces an early hypoglycemic effect followed by hyperglycemia. The initial hypoglycemic effect has not been well explained, however, as the subsequent hyperglycemia appears to be caused by diminished glucose utilization and a decreased sensitivity to insulin. In humans, injections of growth hormone decrease glucose tolerance in normal subjects as well as in diabetic patients (Fig. 1).

Although it appears that growth hormone and insulin have divergent influences on intermediary metabolism, both hormones are required to counteract the nitrogen loss associated with diabetes. Growth hormone, which causes nitrogen retention in normal, hypophysectomized, adrenalectomized, and insulin-treated diabetic animals is partially effective in hypothyroidism but is ineffective in the diabetic not receiving insulin (4). Although a sensitive balance is normally present between the two hormones, insulin favors lipid conservation and carbohydrate utilization at the time of feast whereas growth hormone facilitates lipid utilization and carbohydrate conservation during famine. Both hormones cooperate in conserving the body's critical protein stores during either the fasting or feasting state.

Growth hormone administration to animals with marginal body stores of vitamin A depletes the vitamin faster than would have otherwise occurred (5). Pantothenic acid-deficient rats injected with growth 

![Graph](https://academic.oup.com/ajcn/article-abstract/23/3/311/4716667)

**Fig. 1.** A decrease in the $K$ value of the intravenous glucose tolerance test is observed in normal subjects after injection with human growth hormone.
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hormone develop acute deficiency symptoms (6), and pyridoxine-deficient animals have more severe acrodynia (7). In humans, acromegaly is not usually associated with vitamin deficiency or undernutrition since dietary intake is adequate and actual growth is minimal.

Retention of phosphorus, magnesium, potassium, and sodium is consistently found with administration of growth hormone. The uptake of radioactive sulfate by cartilage is well known and has been used as a laboratory aid in determining growth hormone activity. The effect of growth hormone on calcium metabolism is complex. Although excessive amounts of growth hormone cause hypercalcemia, balance studies in acromegals have given inconsistent results. The levels of serum phosphorus and alkaline phosphatase are usually increased when the disease is active. Osteoporosis is found occasionally in acromegaly in spite of the potent anabolic effects of growth hormone.

About 25% of acromegalic patients develop diabetes mellitus thereby requiring the appropriate nutritional and therapeutic measures accorded all diabetics. Another nutritional concern is the need for salt restriction as heart failure, too, is a frequent complication of acromegaly.

Hypopituitarism

The effects of hypopituitarism on nutrition may be varied as deficits may be partial or confined to an isolated tropic hormone. Panhypopituitarism is associated with a lowered metabolic rate. Anorexia may result in dietary deficiencies. The metabolic needs are sufficiently reduced, however, so that cachexia or marked weight loss is rare. Fat stores are preserved due to the normal and unopposed insulin action that also accounts for the susceptibility of these patients to hypoglycemia.

Absorption of food is impaired with hypopituitarism and gastric secretion is reduced. Pituitary ablation rapidly decreases the volume of gastric secretion to half its previous volume a few days after surgery. Gastric atrophy and decreased numbers of parietal cells are noted in experimental animals (8). Removal of the hypophysis, adrenals, ovaries, or thyroid gland is associated with decreased glucose absorption while little or no change is noted after removal of the testes (9, 10).

Growth is retarded or ceases completely as a result of loss of growth hormone and gonadotropins. Those dietary requirements which depend on the rate of growth are decreased. Protein synthesis is also decreased.

Patients tend to become hypoglycemic when fasting. This is due to lack of the "anti-insulin" and gluconeogenic hormones and the persistent secretion of insulin. An amelioration of diabetes mellitus is noted in patients who develop hypopituitarism. This is primarily due to the lack of growth hormone, cortisol, and thyroid hormones. However, even though cortisol and thyroid hormone are replaced, diabetics require less insulin after hypophysectomy, presumably due to growth-hormone deficiency.

Mineral and electrolyte requirements are not greatly altered in spite of adrenal insufficiency. Aldosterone secretion is not totally dependent upon corticotropin, thus sodium is retained. Hyponatremia may occur in these patients, but it is due to the decreased ability to excrete a water load.

Caloric undernutrition inhibits secretion of the anterior pituitary hormones and may produce symptoms indistinguishable from primary hypopituitarism. Decreased metabolism, developmental failure, gonadal atrophy, and intolerance to stress may develop. Anorexia nervosa, a psychogenic disturbance resulting in severe undernutrition has been frequently confused with hypopituitarism. Amenorrhea is common in both conditions. Patients with anorexia nervosa are alert in spite of ap-
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pearing cachectic. There is preservation of forearm, axillary, and pubic hair, and they are able to respond to metapyrone by increasing steroid excretion indicating an adequate pituitary-adrenal axis (11).

Inhibition of anterior pituitary secretions also occurs if there is a lack of essential amino acids, protein, or vitamins (12–14). The response of the pituitary to a reduced calorie and vitamin intake may well be an adaptive mechanism that permits survival of the individual by decreasing body activity, lowering metabolic rate, retarding growth, and inhibiting gonadal function.

**Diabetes Insipidus**

A deficiency of antidiuretic hormone (vasopressin) results in the persistent excretion of large volumes of dilute urine. An obvious nutritional consequence of this condition is the need for significantly increased water intake to compensate for the polyuria. When copious amounts of water are not taken in, severe dehydration rapidly occurs with hemoconcentration. Little is known about the role of vasopressin on fat and carbohydrate metabolism in man. Experiments performed in animals with an intact pituitary-adrenal axis must take into account the recent evidence demonstrating the ability of vasopressin to act as a corticotropin-releasing factor. This has also been demonstrated in humans.

In children with diabetes insipidus that is poorly regulated, retardation of growth has been reported (16). It has been suggested that these patients have learned that food restriction reduces urinary output by decreasing the solute load. The resultant inadequate nutrition may produce hypocaloric dwarfism. On the other hand, DelVecchio et al. (17) produced a widening of the epiphysyeal cartilage after injection of vasopressin in intact rats which did not occur in hypophysectomized rats. They suggest that a deficiency of vasopressin or some other hypophyseal polypeptide may decrease growth hormone secretion, which causes the dwarfism.

In summary, diabetes insipidus causes an increased need for water. Proper control of the disease is necessary in growing children to avoid hypocaloric growth retardation and in adults to prevent marked polyuria.

Inappropriate antidiuretic hormone secretion manifested by hyponatremia and hemodilution is found in association with nonendocrine tumors, pulmonary tuberculosis, and other disorders. The condition is recognized by increased urinary sodium excretion in spite of hyponatremia. It can be controlled by water restriction.

**Hypothalamic and Posterior Pituitary Abnormalities**

After the description of Froehlich's syndrome in 1901, a search began to incriminate the endocrine glands as the primary cause of obesity. The association of obesity with hypogonadism due to a tumor or other lesion involving the hypothalamus is extremely rare. Overeating and decreased activity are the most important factors in weight gain of this syndrome although the hypogonadotrophic hypogonadism plays a role in the characteristic distribution of fat. Severe hunger develops experimentally if the ventromedial nuclei of the hypothalamus are destroyed. Diet produces weight loss, but due to the ravenous appetite in this condition, voluntary dieting is frequently impossible.

On the other hand, in experimental animals, cachexia and inanition have been produced by destruction of the lateral nucleus of the hypothalamus. Its clinical counterpart has been reported by White and Ross (15) who described malnutrition in infants with tumors of the third ventricle or anterior hypothalamus.

**Thyroid Disease**

The thyroid hormones act on the peripheral cells to regulate oxygen consumption
and heat production in humans. Michels et al. (18), suggested that these effects are due in part to the stimulation of protein synthesis by thyroid hormone. The activity of over 50 intracellular enzymes have been demonstrated to increase, indicating there is no one specific enzyme responsible for the action of thyroxin.

All mammals require thyroid hormone for normal growth and maturation. When secreted in proper quantities, protein synthesis proceeds normally.

**Iodine in Thyroid Disease**

An outstanding example of a nutritional deficiency affecting endocrine function is the role of iodine upon the thyroid gland. Approximately 200 million people throughout the world have goiter of some degree. Although iodine deficiency accounts for most of these, other factors such as inherited enzymatic defects in hormone synthesis and ingestion of goitrogenic substances play a role. Iodine is an essential nutrient for man. Its main function is concerned with the formation of the thyroid hormones. After absorption from the intestine, iodine is transported in the blood as the iodide. The great avidity of the thyroid cell for iodide causes it to be trapped there, oxidized to elemental iodine, and then incorporated into an amino acid, tyrosine, which in a series of coupling reactions becomes the active hormone, triiodothyronine and tetraiodothyronine (thyroxine).

During the last Ice Age vast areas of the world were left with a new soil created by the grinding up of crystalline rock. The new soil is iodine poor in comparison to the soil that it replaced. This has been a problem in the Alps, the Pyrenees, the Great Lakes Basin, the Thames Valley in England, and many parts of China and Japan. Many patients with endemic goiter and cretinism are found in these regions. In Japan, the prevalence of endemic goiter is quite low because of the peoples' dietary preferences for iodine-rich seaweeds and fish. Before the discovery of iodine, seaweed and fish were empirically used in the treatment of goiter.

In 1921 Marine and Kimball (19) presented their classical work implicating iodine deficiency as a major etiologic factor of goiter and showing the beneficial effect of its replacement. The prevalence of goiter in four counties of Ohio was 40% in 1925. Hamwi et al. (20) surveyed the same area in 1954 and found goiter in only 4% of schoolchildren, again demonstrating the efficacy of supplemental iodine in preventing goiter. A deficient intake of iodine results in hyperplastic changes in the thyroid gland followed by distention of the follicles with colloid. Iodine prevents and may reverse most of these abnormalities.

The optimal adult requirement for iodine is approximately 200–300 
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\text{mg/day}. \\
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In the United States, iodized salt contains 0.01% potassium iodide. Thus the requirement could easily be satisfied on an intake of 3–4 g salt daily. In some areas of the United States, the major source of iodine is iodized salt; therefore, supplements may be necessary in persons for whom low salt diets are prescribed. Modern transporting and freezing techniques provide an increasingly important source of iodine containing foods from coastal areas. Conditions such as pregnancy, lactation, infection, puberty, and acromegaly increase requirements considerably above those of the normal adult.

Prolonged and excessive intake of iodine may interfere with hormone synthesis. The compensatory thyrotropin stimulation may produce a diffuse nontoxic goiter or hyperthyroidism (21). Correction of the excess iodides usually results in a return to normal. On the other hand, localized toxic effects by the rapid concentration of iodine in the hyperplastic glands may cause acute thyroiditis (22). Thus, as with virtually all nutrients, a proper
amount is desirable, but excessive or inadequate amounts may be detrimental.

Thyrotoxicosis

Hyperthyroidism is a good example of an endocrine disorder with a profound effect upon nutrition. It increases the need for all dietary nutrients. The calorigenic effects of excessive thyroid hormone are wasteful to the body economy. Hypermetabolism occurs in almost all organs except the spleen, brain, and testes.

Hyperthyroid patients may require 2-3 times the normal daily calorie requirement in order to maintain body weight. Intestinal absorption is stimulated directly by thyroid hormones. Carbohydrates are more rapidly absorbed. Many of the enzymatic reactions are accelerated. When secreted in proper quantities, the effect of thyroid hormone on protein metabolism is that of synthesis and nitrogen retention. Excessive amounts, however, result in greater catabolism of protein with gradual wasting of the lean body mass. Kekki (23) reported that both synthesis and catabolism of albumin are accelerated with little change in the total albumin mass.

The effect of excessive thyroid hormone on fat is catabolic. Most patients lose weight since their intake is insufficient to compensate for the increased metabolic needs. Fat is mobilized from depot stores, plasma free fatty acids may initially increase. Excessive thyroid hormone lowers serum cholesterol, phospholipids, and triglycerides. Alpha- and beta-lipoproteins are decreased (24). The fall in serum cholesterol level is best explained by increased degradation and biliary excretion of cholesterol.

Thyroid hormones elevate blood levels of glucose after a meal by increasing glucose absorption. They also potentiate the epinephrine effects on glycogenolysis. These combined effects decrease glucose tolerance. An adequate insulin reserve prevents a major alteration of blood sugar in most hyperthyroid patients (25).

Utilization of glucose is enhanced in the hypermetabolic cells, which may lead to glycogen depletion. For this reason it is unwise to limit carbohydrate intake because of an abnormal glucose tolerance test. The decreased glucose tolerance may persist after achieving an euthyroid state (26).

Hyperthyroidism increases the need for almost all the vitamins especially pyridoxine, pantothenic acid, and thiamin. When these vitamins are provided, hyperthyroid animals are able to regain some weight (27). A deficiency of pyridoxine in a normal animal depresses the uptake of radioactive iodine by the thyroid gland. The derangement of tryptophan metabolism, as evidenced by increased urinary excretion of xanthurenic acid in hyperthyroid patients, can be corrected with pyridoxine (28). If pyridoxine deficiency exists, gastric secretion decreases with a subsequent decline in vitamin B<sub>12</sub> absorption. Eventually experimental animals become deficient in vitamin B<sub>12</sub> even though adequate amounts are offered in the diet. This illustrates the importance of absorptive abnormalities, in this case due to a deficiency of one vitamin, resulting from a disorder of an endocrine gland.

Recently, Mohamed and Roberts (29) have reported that seven of ten thyrotoxic patients showed an abnormality in the breakdown of histidine to glutamic acid. This reaction has been shown to be folate dependent and suggests that a relative deficiency of folic acid exists in the thyrotoxic patient. Similarly, excessive thyroid secretion has been demonstrated to increase the need for vitamin A, riboflavin, ascorbic acid, vitamin D, choline, and perhaps vitamin E (30).

Serum and urinary calcium levels are mildly elevated, and a negative calcium balance exists. Urinary losses of phosphorus are even greater than calcium. Total body magnesium is low in spite of normal or
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high serum levels (31). Losses of potassium in the urine depend upon the extent of protein catabolism. Muscle weakness due to hypokalemia may be severe, and periodic paralysis has been precipitated or made worse by thyrotoxicosis (32). Mineral absorption from the gut can compensate for excretory losses if adequate amounts are in the diet. Osteoporosis, especially in the postmenopausal female, is the result of increased mobilization and excretion of calcium and the increased catabolism in the protein matrix of bone.

*Hypothyroidism*

The depressed metabolic rate in hypothyroidism is accompanied by a poor appetite, decreased gastric secretions, constipation, and a decrease in intestinal absorption. Many of the nutritional requirements are decreased in hypothyroidism and fewer calories are needed to maintain body weight. Although obesity occurs in hypothyroid patients, it has been overemphasized in the past. The myxedematous patient does retain fluid and develops a peculiar type of nonpitting edema, rich in mucopolysaccharides, which accounts for some of the weight gain.

Hypothyroidism decreases the synthesis of proteins from amino acids. Nitrogen excretion is decreased. The lowered metabolic rate influences the secretion of other hormones. Adrenal and pituitary hormones decrease in association with hypothyroidism. Androsterone, one of the major end products of testosterone metabolism, is diminished, thus its weak anabolic effect on protein as well as its ability to lower lipoprotein levels is lost (33). The effects on protein metabolism are, therefore, influenced not only by lower levels of circulating thyroid hormones, but by altering the actions of other hormones as well.

Hypothyroidism is associated with an elevation of the serum cholesterol. Although the rate of incorporation of acetate into cholesterol is reduced, so is its breakdown. The net result is an increase in total serum cholesterol. Thyroid deficiency affects the entire lipoprotein spectrum causing elevation of the triglycerides as well as the serum cholesterol (34). Plasma free fatty acid concentrations are usually not significantly different from normal. They are, however, used less efficiently than in normal persons (35).

Carbohydrate metabolism is also affected in hypothyroidism. Glucose is absorbed slowly from the intestine resulting in a flat glucose tolerance curve. Hypothyroidism ameliorates existing diabetes mellitus and lowers insulin requirements. The increased sensitivity to insulin is associated with occasional hypoglycemic reactions. In general, blood glucose levels do not change in most cases of thyroid deficiency.

Vitamin deficiencies are rarely a problem since the metabolic demands of the body are low. Vitamin B12 supplementation improves the growth of experimental animals made hypothyroid. In humans, a mild anemia is found in the majority of patients with thyroid deficiency. The anemia may be hypochromic, megaloblastic, normochromic, or normocytic. A few patients respond to vitamin B12; the others require iron or treatment with thyroid hormone. Vitamin A is formed in the body from carotenoid precursors of which β-carotene is the most efficient. Thyroid hormones facilitate the conversion of the carotenes to vitamin A. When thyroid insufficiency exists, hypercarotenemia may develop imparting the yellow discoloration to the skin of myxedematous patients.

Mineral metabolism in hypothyroidism in regard to iodine has been discussed. In general, no significant losses of minerals occur in the urine, although a decrease in the protein-bound magnesium may be seen. Iron absorption tends to decrease.
In summary, hypothyroidism reduces the requirements of many nutrients. The effects upon lipid metabolism have been of interest because of the elevation of serum lipids. Iodine supplementation has been a major accomplishment in the prevention of endemic goiter and cretinism. Hypothyroidism reduces iron and vitamin B₁₂ absorption and at least some of the associated anemias can be corrected by the appropriate nutrient. Thyroid replacement therapy readily corrects the basic deficiencies of hypothyroidism.

PARATHYROID DISORDERS

The active hormone of the parathyroid gland, parathormone, has as its chief function the control of calcium levels in body fluids. Secretion of the hormone results in an increase in the serum calcium. In the normal person a negative feedback mechanism exists whereby hormone release is inhibited by an increase in the concentration of ionized calcium.

Parathormone increases bone resorption, calcium absorption from the gut, and renal tubular calcium reabsorption. The increase in serum calcium often, but not invariably, exceeds the ability of the tubules to reabsorb calcium resulting in hypercalciuria and a negative calcium balance.

Calcium is one of the principal elements of the structural skeleton. It is found in bone as the apatite salt. The calcium in bone is in equilibrium with that in the extracellular fluids and is readily mobilized when the serum concentration falls. Calcium serves several other major functions. It is required for the normal clotting of blood, and a normal concentration is essential for the optimal function of nervous tissue. Muscle contractility is also dependent upon an optimal calcium concentration.

The interrelationship of parathormone, calcium, and vitamin D is exemplified in nutritional rickets. When vitamin D is deficient, calcium absorption is inadequate and serum levels fall; parathroid hormone secretion is stimulated, and calcium is mobilized from bone in order to maintain normal blood levels. Demineralization of bone results, which produces the clinical picture of rickets in children and osteomalacia in adults. Hyperplasia of the parathyroid glands in rickets suggests that secondary hyperparathyroidism plays an important role in both the biochemical and skeletal lesions that one sees.

Calcitonin is a recently described polypeptide hormone from the thyroid gland that lowers serum calcium and phosphate. Copp and his co-workers (36) reported in 1962 that a hormone released from parathyroid glands lowered blood calcium rapidly in response to hypercalcemia. Subsequent studies have shown this hormone to be released by cells derived from the last pharyngeal pouches in lower animals and by thyroid cells in humans presumably originating from the same source. Therefore, the term, thyrocalcitonin, is commonly used by some workers instead of calcitonin.

The hormone, a polypeptide with a molecular weight of 3,600 and known amino acid sequence, lowers serum calcium by inhibiting bone resorption while calcium continues to enter bone (37). Apparently, feed-back mechanisms dependent upon serum calcium concentrations exist that involve calcitonin and parathormone. Hypercalcemia stimulates thyroid parafollicular cells to secrete calcitonin resulting in a lowering of the calcium concentration, while hypocalcemia causes parathormone to be released from the parathyroid to effect a rise in the level of calcium.

High concentrations of material similar to calcitonin have been found in medul- lary carcinoma of human thyroid (38). The tumor cells resemble the parafollicular cells of normal thyroid gland and may represent the source of the "hypocalcemic"
activity in such patients. Other conditions characterized by unexplained hypocalcemia, such as pseudohypoparathyroidism, may be associated with abnormal calcitonin secretion.

The effects of vitamins and other minerals upon calcitonin remain generally unknown. Since vitamin D is so intimately related to calcium metabolism, it is not surprising that its effects on calcitonin-producing cells are under active investigation. There is possibly a close link between the metabolism of iodine and that of calcium. Iodine is present in extracts of thyrocalcitonin (39). There is a good correlation between the amount of iodine in an extract and the potency of the hypocalcemic effect. There are as yet no proved clinical abnormalities associated with calcitonin. Its role in the physiologic and therapeutic control of calcium metabolism, its effects upon nutrition, and its interrelationships with other hormones are all intriguing aspects that are being studied in laboratories throughout the world.

**Hyperparathyroidism**

An overproduction of parathormone results in a rise in serum and urinary calcium at the expense of bone demineralization. If the calcium intake is adequate, bones may remain grossly normal. If it is insufficient, osteitis fibrosa generalisata may develop.

It is difficult to determine the prevalence of hyperparathyroidism because of the wide spectrum of nonspecific clinical manifestations associated with it. The most obvious symptoms are those due to renal calculi. Peptic ulcer, as well as the classical but increasingly less frequent, bone lesions are also seen.

Appetite, absorption, and utilization of food in hyperparathyroidism may be altered due to the gastrointestinal disturbances that are frequently present. Pancreatitis, which has been reported to be associated with hyperparathyroidism (40) could affect nutrition by causing anorexia, abdominal pain, intolerance to certain foods, malabsorption, and weight loss. Parathormone increases calcium absorption from the intestine. Absorption is facilitated by the presence of vitamin D and a low intestinal pH that keeps the calcium in solution.

Elevated serum calcium levels result in inhibition of the action of antidiuretic hormone on the renal tubule with resultant excessive water excretion. Occasionally a mild acidosis, probably a consequence of defective hydrogen ion excretion, is observed (41).

Excessive secretion of parathormone has a marked catabolic influence on body protein. Landau and Kappas (42) have presented well controlled metabolic studies demonstrating the nitrogen wasting effects of parathormone in spite of a seemingly sufficient diet. The anabolic hormones (growth hormone, testosterone, and estrogen) decrease the excessive tissue destruction.

In hyperparathyroidism excessive excretion of inorganic phosphate, calcium, and potassium occurs. Although urinary magnesium losses are increased, deficiency does not usually become evident until surgical correction of the hyperparathyroidism. An accentuated deposition of magnesium in the bones then occurs. If the body stores are low, symptoms indistinguishable from hypocalcemic tetany occur. Magnesium replacement is imperative for correction of these symptoms.

In summary, hyperparathyroidism can affect nutritional needs by its association with peptic ulcer or pancreatitis. Catabolic effects upon protein and bone structure are profound and supplemental calories, protein, magnesium, and potassium are needed. Supportive care and anabolic agents are helpful in the management of the hyperparathyroid patient, but surgical correction of the underlying condition is the ultimate therapeutic aim.
Hypoparathyroidism

Deficiency of parathormone results in hypocalcemia, decreased urinary excretion of calcium, and an elevated serum phosphorus. Tetany is the most prominent clinical manifestation of acute hypocalcemia. However, adaptation to hypocalcemia may occur, since tetany occurs rarely in chronic hypocalcemic states.

Hypoparathyroidism is associated with decreased intestinal absorption of calcium. The rate of bone resorption is decreased as is the uptake of calcium by bone.

Therapy with large doses of vitamin D (50,000–300,000 units daily) and a diet containing 1,000 mg/day calcium usually suffice to maintain serum calcium at normal levels. A high calcium, low phosphate diet has traditionally been used in the treatment of hypoparathyroidism. Milk products and egg yolks are high in phosphate as well as in calcium. It has not been conclusively demonstrated, however, that these foods should be restricted in hypoparathyroidism. Patients vary considerably in their response to vitamin D and calcium and, therefore, optimal replacement must be individualized by careful assessment of the patient until serum calcium levels stabilize. We have found that many patients require less vitamin D during the summer months presumably due to exposure to sunlight. In hypoparathyroidism secondary to thyroid surgery, thyroid replacement is also necessary to assure optimum absorption of calcium.

Adrenal Disorders

The vital function of the adrenal glands was not fully appreciated until Addison’s description in 1855 of the clinical manifestations associated with destruction of the glands. Studies later determined that the cortex secreted the life-maintaining hormones since the medullary catecholamines could not sustain life in the animal with adrenal insufficiency.

Adrenal disorders not only affect nutrition, but the adrenals are quite sensitive to nutritional abnormalities. That adrenal cortical function is increased in many obese patients is now well known. The mean cortisol secretion rate in normal adults is 18 mg/24 hr and 28 mg/24 hr in grossly obese individuals. Schachner et al. (43) reported that short periods of starvation reduced urinary excretion of 17-hydroxycorticoids, 17-ketosteroids, and unconjugated 11-hydroxycorticoids. The reduction is probably mediated by decreased corticotropin secretion.

Many vitamin deficiencies can alter adrenal function. Since the ascorbic acid level is high in adrenal cortex, one tends to conclude that it is utilized there. Many symptoms of scurvy, i.e., fatigue, loss of muscle strength, digestive disorders, and reduced ability to tolerate stress resemble those of adrenal insufficiency. Glucocorticoids can modify these symptoms. There seems to be an inefficient utilization of steroids in the absence of adequate ascorbic acid.

Vitamin A deficiency causes both structural and functional changes in the adrenal gland (44). The interference of gluconeogenesis in vitamin A deficient animals is probably an indirect effect of the vitamin lack and more directly related to adrenal insufficiency.

Hyperfunction of the Adrenal Cortex

The excessive secretion of adrenocortical hormones produces nutritional and metabolic changes that depend upon the type of hormone produced. Cushing’s syndrome is essentially the expression of excessive glucocorticoids.

The effect of cortisol on absorption of foods is not entirely clear. From the evidence available, it appears that prolonged administration results in increased gastric secretions, whereas acute experiments often show no change (8). Although some hormone is necessary for normal absorption
of carbohydrates, excessive amounts do not alter absorption significantly (10).

In Cushing's syndrome due to hyperplasia of the adrenal cortices, there is fluid retention, hypernatremia, and hypokalemia, in spite of normal levels of aldosterone. A metabolic alkalosis that is the result of potassium and hydrogen ion losses in the urine is often present. The losses are directly related to the amount of cortisol secreted. Appetite is usually stimulated and, therefore, a weight gain frequently occurs.

Protein metabolism is profoundly affected in Cushing's syndrome. Gluconeogenesis, a major metabolic effect of the glucocorticoids, is enhanced. This results in protein catabolism. Amino acids are then available for conversion to glucose. Increased nitrogen excretion is the result of protein breakdown. The catabolic effects of glucocorticoids are evident in the patient. Striae, due to loss of subcutaneous connective tissue; osteoporosis, due to the loss of protein matrix of bone; and wasting of the extremities, due to muscle atrophy are characteristic findings. Nitrogen losses may be associated with an aminoaciduria. Protein supplementation may decrease the losses. Albanese et al. (45) have reported that the addition of 600 mg L-lysine to the diet of patients taking steroids decreases the catabolic effects if the protein intake exceeds 88 g/day.

As a result of the potent gluconeogenic effect of cortisol, an increase in blood sugar and glycogen stores occurs. Hyperglycemia causes increased insulin secretion. Eventually islet cell reserves may become depleted and "steroid diabetes" ensues. Preexisting diabetes mellitus is made worse by excessive cortisol and is characterized by increased insulin requirements. Thus, the hormone that maintains normoglycemia during the fasting state, when secreted excessively, frequently results in diabetes mellitus.

The effects of Cushing's syndrome on fat metabolism are principally permissive ones. Experimentally, hydrocortisone increases lipogenesis in the epididymal fat pad, the carcass, and the heart. In humans, glucocorticoids induce a centripetal redistribution of fat with excessive deposition in the face, neck, and trunk. Dorsal kyphosis resulting from osteoporosis and the increased supraclavicular fat pads give rise to a "buffalo hump." The fat deposits are probably mediated by the lipogenic action of insulin, which supersedes the weaker lipolytic and lipogenic-inhibiting effects of the glucocorticoids (46). Hypercholesterolemia is frequently found in patients with Cushing's syndrome.

Experimental data suggest that Cushing's syndrome increases the need for various vitamins. The conversion of carotene to vitamin A is inadequate in cortisone-treated animals (47). Vitamin B_{12} and thiamin deficiencies are accentuated when steroids are administered (30). The requirement of pyridoxine, which is the cofactor of one of the enzymes (glutamic pyruvic transaminase) utilized in gluconeogenesis, is also increased significantly (13).

Excessive adrenocorticoids cause marked changes in electrolyte requirements. Potassium losses in the urine are excessive and hypokalemic alkalosis results. Sodium is retained due to the mineralocorticoid action of the hormones. Hypertension is common in Cushing's syndrome. A negative calcium balance also exists. Calcium losses combined with protein breakdown of the bone matrix results in osteoporosis. This is a major problem in patients taking cortisone for a long period of time (48). A higher calcium intake may protect steroid-treated patients from osteoporosis.

In summary, protein catabolism, excessive gluconeogenesis, and electrolyte losses due to excessive glucocorticoids result in increased nutritional requirements. Appetite is usually stimulated and weight is
maintained or increased. Additional dietary proteins, essential amino acids, calcium, potassium, and vitamins may retard the destructive consequences of the disease. As with other endocrine abnormalities, therapy must be directed to the underlying disorder.

**Hyperaldosteronism**

The recognition of this condition has become one of major importance in the field of hypertension. Aldosterone has a potent mineralocorticoid influence with very little glucocorticoid function at physiologic levels. Aldosterone stimulates RNA synthesis of various enzymes that participate in sodium transport (49). Excessive secretion leads to sodium retention and potassium losses by the renal tubules, sweat glands, and other secreting glands. The resulting hypokalemia is associated with a metabolic alkalosis.

Glucose tolerance is often decreased in hyperaldosteronism. This may be due to the hypokalemic effect on the cell resulting in less peripheral glucose utilization or an inhibition of insulin secretion.

In humans a negative magnesium balance is found in primary aldosteronism. Increased magnesium excretion is due to a direct action of the hormone (50). Potassium and calcium losses occur in the feces and urine, and an adequate intake of potassium, water, magnesium, and calcium are required to improve the patient's condition until the primary cause of increased aldosterone secretion can be eliminated.

**Addison's Disease**

The primary defect in Addison's disease is a deficiency of all adrenocortical steroids. Weakness, weight loss, dehydration, and the inability to withstand stress are characteristic features. Anorexia is common as well as nausea, vomiting, and diarrhea. There is some evidence to indicate that malabsorption also occurs. Dehydration contributes to the weight loss, which is frequently severe.

Adrenocortical insufficiency often produces hypoglycemia in untreated patients. There is decreased carbohydrate adsorption and a deficiency in "new glucose" formation. Glucocorticoids increase gluconeogenesis from the products of protein breakdown and inhibit utilization of glucose. This is accomplished by 1) increasing mobilization of protein by way of amino acids to the liver for later transamination and conversion into glucose; 2) facilitating liver glucose production from three-carbon precursors; and 3) selectively increasing glucose 6-phosphatase activity resulting in less available glucose 6-phosphate for glycolysis (51).

The amelioration of the diabetic state following adrenalectomy was noted by Hartman and Brownell in 1934 (52). Long and Lukens (53) later showed the same response in the cat after either hypophysectomy or adrenalectomy. They concluded that a decreased production of glucose and ketone bodies occurred rather than a resumption of normal carbohydrate utilization.

Recently, we reviewed the clinical records of 41 patients with Addison's disease and found that the prevalence of overt diabetes mellitus was 17% (54). The association of diabetes and Addison's disease is higher than expected in view of the tendency towards hypoglycemia with adrenal insufficiency.

Although the requirement of vitamins in Addison's disease is not altered significantly, a number of experiments indicate that vitamins may alter cortisol metabolism. Vitamin B complex increases the survival of adrenalectomized rats. Ascorbic acid retards the degradation of cortisol and thus increases the availability of the hormone.

Depletion of sodium and retention of potassium occurs in untreated Addison's disease. Hypercalcemia may be seen, but
this finding is not common (55). Hypermagnesemia is associated with Addison's disease and results in depression of the central nervous system and peripheral neuromuscular function.

In summary, adrenocortical insufficiency results in hyponatremia and hyperkalemia. Weight loss is due to anorexia, dehydration, and decreased intestinal absorption. A defective mechanism for gluconeogenesis exists. Supplemental sodium chloride and a diet that provides sufficient carbohydrate, protein, and vitamins should be prescribed. Prolonged fasting should be avoided in patients with Addison's disease. Replacement therapy with cortisol and a mineralocorticoid is, of course, mandatory and will correct the deficits.

**Pheochromocytoma**

The effects of excessive catecholamine secretion are striking. Dietary needs depend upon the extent of the hypermetabolic state. Hypertension, sweating, headaches, anxiety, nausea, vomiting, and anorexia are usual manifestations during adrenosympathetic crises.

Weight loss in patients with the disease occurs because of the anorectic effect of the catecholamines as well as the elevated metabolic rate. Epinephrine has an inhibitory effect upon the motility of the gastrointestinal tract. Absorption of food is not affected significantly except when abdominal pain and vomiting are present. Dietary requirements are increased because of the hypermetabolic state.

The effects of high levels of catecholamines on protein metabolism are indirect. Increased nitrogen excretion is detected in patients with active disease. Epinephrine acts as a nonspecific stress and activates the pituitary–adrenal axis. This effect would tend to increase catabolism of protein as an accompaniment of gluconeogenesis.

Both epinephrine and norepinephrine are potent lipolytic agents and free fatty acids are released from body fat stores in their presence. By blocking free fatty acid release with nicotinic acid, the calorigenic response of catecholamines is reduced, although not abolished. Endogenous stores of lipid are probably also oxidized and contribute to the heat produced by catecholamines (56).

The effects of pheochromocytoma on carbohydrate metabolism are diabetogenic. Epinephrine induces hyperglycemia by activating phosphorylase, an enzyme active in glycogenolysis. Epinephrine decreases glycogen in both liver and muscles. Increased amounts of lactic acid are produced. Inhibition of insulin secretion by the catecholamines contributes to the hyperglycemia.

Persistence of the disorder results in severe hypertension. It may ultimately produce kidney disease. Electrolyte and water requirements must then be adjusted to meet the new demands. Again, the primary therapy is surgical removal of the tumor or the use of pharmacologic agents to inhibit the formation or action of catecholamines.

In summary, a pheochromocytoma produces an increased metabolic rate, increased lipid breakdown, and hyperglycemia. These changes result in an increase in most of the nutritional requirements until the underlying condition can be corrected.

**Disorders of the Gonads**

The testes and ovary, although essential for reproduction, are not vital to the individual. The gonadal hormones, however, exert many generalized metabolic effects in addition to their specific actions on the sex organs.

The major metabolic actions of the androgens and estrogens are compared in Table 1. Progesterone modifies the metabolism of estrogens and perhaps exerts some of its actions in this way. Alone, however, it causes protein catabolism. Be-
Hamwi and Tzagournis

Table 1

<table>
<thead>
<tr>
<th>Androgens, strongly anabolic</th>
<th>Estrogens, weakly anabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td></td>
</tr>
<tr>
<td>Increased free fatty acid mobilization</td>
<td>Increased lipogenesis, especially in breasts, buttocks, and thighs</td>
</tr>
<tr>
<td>Increases oxygen consumption</td>
<td>Decreases oxygen consumption</td>
</tr>
<tr>
<td>Decreases fat stores in relation to lean body weight</td>
<td>Increases fat stores in relation to lean body weight</td>
</tr>
</tbody>
</table>

| Lipids                        |                             |
| Increased δ-lipoprotein (cholesterol) | Decreases δ-lipoprotein (cholesterol) |
| Decreases α-lipoprotein (phospholipids) | Increases α-lipoprotein (phospholipids) |
| Increases sebum               | Decreases sebum             |

| Carbohydrates                |                             |
| Possibly antidiabetogenic    | Questionable significance    |
| Retains sodium               | Retains sodium              |
| Retains potassium            | Retains potassium           |
| Retains phosphorus           | Retains phosphorus          |
| Retains calcium              | Retains calcium             |

Anemia, dwarfism, hypogonadism, and hepatosplenomegaly is described in a group of patients by Prasad et al. (57). Biochemical studies suggested to the authors that zinc deficiency is a principal factor in the syndrome. Experimental animals fed zinc-deficient diets show testicular atrophy.

Experimental animal work can be helpful in the study of nutrition-hormone interrelationships in humans. There exists, however, considerable species difference. A deficiency of vitamin E, for example, produces marked changes in the gonads of rats, but its effects upon human gonads have not been conclusively shown.

**Hypogonadism in Females**

Ovarian failure may occur as a congenital condition or as the menopause, the most physiologic example. The clinical and nutritional effects are due primarily to estrogen deficiency.

Estrogens are steroids that arise from the ovary, adrenal cortex, the Leydig cells of the testis, and placenta. The human ovary secretes primarily estradiol and estrone, although many other metabolites have been isolated from human urine and blood. The mechanism by which estrogens exert their influence is unknown.
Permeability of a target cell membrane may be altered, and thus metabolically active substances can pass into and out of the cell. They may function by acting upon enzyme systems, either directly participating in metabolic reactions or acting as stimulants for the synthesis of protein enzymes.

A deficiency in female sex hormones reduces the rate of intestinal absorption of glucose and possibly other nutrients. Estrogens decrease gastric acid secretion slightly and may account for the lower incidence of peptic ulcer during the reproductive life of the female as compared to the male. Obesity is a frequent problem in patients with ovarian dysgenesis. In general, estrogens have their greatest anabolic effect on the secondary sex glands, a lesser effect on the protein matrix of bones, and little or no effect on other body protein.

Progesterone in amounts usually secreted in pregnancy is catabolic to body protein. The two hormones together tend to cancel the individual effects of each (58).

Lipid metabolism is influenced by the levels of estrogen. Obesity is more common in females than in males. Fat distribution is affected as evidenced by increased deposition in characteristic body areas during puberty in the female. The direct role of estrogen in influencing this distribution is not clear. Estrogens reduce serum cholesterol and beta-lipoproteins, but increase the alpha-lipoproteins slightly. In patients with hyperlipidemia, the administration of estrogens decreases cholesterol, phospholipids, and triglycerides (59). These findings have led to the use of estrogens in various clinical conditions, especially coronary heart disease. Although serum cholesterol can be lowered, there is as yet no conclusive evidence that regression in well developed atherosclerosis occurs. In postmenopausal females, however, symptoms due to vasomotor instability, osteoporosis, atrophy of the genital mucosa, and emotional instability may be improved by treatment with estrogens.

In the human the prevalence of diabetes is equal in the two sexes during childhood and adolescence, but then increases in females in later life. Whether or not this phenomenon is related to estrogen is unclear. Sedentary work with a high food intake may encourage obesity and a greater tendency toward diabetes.

Decreased sex hormones cause some changes in mineral metabolism. A major effect is on bone, which indirectly affects calcium. Lack of estrogen in the young female delays union of the epiphyses, and a relative overgrowth of long bones occurs. In the postmenopausal female calcium losses increase and are probably the result of increased bone catabolism rather than decreased bone formation. A high intake of calcium partially corrects the losses (60). The administration of estrogen usually results in retention of sodium chloride, water, and calcium. Progesterone produces sodium loss and potassium retention due to its competitive inhibition with aldosterone, a potent salt retainer. If progesterone is given in sufficiently large doses to produce protein catabolism, potassium losses may ensue.

In summary, hypogonadism in the female is associated with a mild protein catabolism, especially of the bone matrix. Increased protein and calcium intakes may be helpful. Estrogen deficiency tends to elevate serum cholesterol and beta-lipoproteins. Replacement of estrogens is indicated in females with hyperlipidemia, osteoporosis, vasomotor instability, and atrophic changes of the genital tract.

**Hypogonadism in Males**

Androgens are substances that have the ability to maintain secondary sex characteristics of the male. The most active androgen is testosterone, which is secreted by the Leydig cells of the testis. The an-
Consequent gen amounts skin, and about poor, characteristics. D!itiOml A has somal stimulates a taming mechanism ne, mass, There Gmowii 326 cure younger growth decreases. In complete several if androgens have many biological effects. Growth of sex specific tissues is stimulated. There is also an increase in general body mass, skeletal structures, muscles, kidney, and specific hair growth. The exact mechanism of action of androgens has not been fully elucidated. The nitrogen retaining action of androgens appears to be a general one affecting many tissues. Kochakian (61) suggests that testosterone stimulates the formation of specific ribosomal RNA to provide increased sites for the formation of templates where messenger RNA can be accepted.

A decrease in androgenic hormones has several important clinical consequences. A complete loss of hormone before puberty produces a peculiar body habitus in addition to absence of secondary sex characteristics. A delay in epiphyseal closure produces lengthening of long bones with consequent prolongation of the active growth period. Muscle development is poor, and prominent fat deposits develop about the breasts, abdominal wall, hips, and buttocks. Other findings are a pallid skin, high pitched voice, and scanty growth of facial and body hair. Fat deposition increases while total lean body protein decreases.

In the hypogonadal patient adequate amounts of protein, calcium, and vitamins are needed to make up losses that occur as a result of catabolism. Watkin et al. (62) studied the effect of androgen administration on the retention of nitrogen, potassium, phosphorus, and calcium on both low and high protein diets. Nitrogen retention is clearly dependent upon protein intake.

When deficiency of testosterone exists, growth and maturation cease in the younger individual. In older persons protein catabolism exceeds anabolism. Nitrogen retention, increased muscle development, and increased protein synthesis occur if androgens are provided. Lipid metabolism is affected by low levels of androgen. Male castrates tend to have low serum cholesterol levels. Furman et al. (63) reported that in dogs, androgens caused a decrease in the total lipids. The authors suggest that the anabolic effect of androgens causes less amino acids to be available to form lipoproteins, by increasing their incorporation into muscle protein. Androgens have fat-mobilizing properties, releasing free fatty acids from the breakdown of adipose tissue (64). During puberty it is usual to see a decrease in the adipose tissue of the male, whereas in the female the tendency is for an increased deposition in selected areas.

Testosterone deficiency does not appear to alter carbohydrate metabolism significantly. Androgen administration has been shown to improve diabetes mellitus but does not have an affect on the blood sugar of a normal person. Methandienone, an anabolic steroid with reduced androgenic effects, causes a fall in the fasting level of glucose in normal subjects; it increases the plasma insulin response to tolbutamide (65). As noted previously, the prevalence of diabetes mellitus is lower in adult men than in women. It remains unclear whether this is due to the presumably beneficial effect of the androgens on blood sugar.

Hypogonadism decreases the needs of vitamins and minerals that depend on the rate of growth. Androgens have weak salt-retaining properties and produce a positive calcium balance in man.

In summary, testosterone is a potent anabolic hormone. Its absence retards protein synthesis in muscles, bones, and other organs. Androgens favor the development of lean body protein at the expense of fat breakdown. The anabolic effect of androgens is dependent upon an adequate intake of calories, protein, vitamins, and minerals.
Nutrition and Diseases of Endocrine Glands

SUMMARY

A close relationship exists between hormones, the regulators of metabolic processes, and nutrition. Not only do excesses or deficiencies of various nutrients affect the function of the endocrine glands, but hormonal abnormalities often alter the absorption, metabolism, and requirements of the various nutrients.

The effects of endocrine abnormalities on nutrition are best exemplified by the generalized increased requirements in hyperthyroidism and acromegaly and the rather specific increased requirement of vitamin D and calcium in hypoparathyroidism.

Hormonal excesses or deficiencies, by altering the various factors of nutrition, demand homeostatic changes for the vital metabolic processes to go on. An increased intake of a nutrient may enable metabolic homeostasis to occur in spite of an abnormal hormonal environment.

REFERENCES

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59. Feldman, E. B., C. Wang and D. Aldersberg. Effect of prolonged use of estrogens on circulat-


