CHAPTER 5

EFFECTS OF THE ENVIRONMENT, CHEMICALS AND DRUGS ON THYROID FUNCTION

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ABSTRACT

The sensitive and tightly regulated feedback control system, thyroid gland autoregulation, and the large intrathyroidal and extrathyroidal storage pools of thyroid hormone serve to provide a constant supply of thyroid hormone to peripheral tissues in the face of perturbations imposed by the external environment, chemicals and drugs, and a variety of diseases processes. The thyroid is subject to a great number of exogenous and endogenous perturbations*.* The same agent may produce alterations in various aspects of thyroid hormone economy. For this reason, it is difficult to precisely classify all external and internal influences according to their mode of action. This chapter reviews effects on the thyroid produced by changes in the external environment, chemicals and drugs. The effects of non-thyroidal illness are reviewed in Chapter 5b. The effects of the more important factors and chemical agents and drugs are discussed individually.

RESPONSES TO ALTERATIONS IN THE EXTERNAL ENVIRONMENT

Environmental Temperature

Changes in environmental temperature may cause alterations in TSH secretion and in the serum concentration of thyroid hormones and their metabolism. The changes are probably mediated through the hypothalamus and the pituitary and by peripheral effects on the pathways and rates of thyroid hormone degradation and fecal losses and alterations in thyroid hormone action. The in vitro effects of temperature on the firmness of binding of T4 to its transport serum proteins conceivably also play a role in vivo.[1] The overall effects of environmental temperature have been more obvious and easier to demonstrate in animals than in humans but differences in thermal regulation [1a] may mean that findings in animal models may not apply to humans. Additionally, studies of individuals with prolonged residence in Arctic and Antarctic regions may be confounded by other alterations in daylight, activity levels, living conditions and sleep deprivation. [1b,1c]

Effects of Cold

Dramatic, although transient, increases in serum TSH levels have been observed in infants and young children during surgical hypothermia.[2] Also, a prompt and important secretion of TSH occurs in the newborn, in the first few hours after birth, accompanied by an increase in thyroid hormone secretion and clearance.[3,4] Since this TSH surge is partially prevented by maintaining infants in a warm environment, postnatal cooling appears to be responsible in part for the rise in TSH secretion. In most studies*,* exposure of adults to cold or even intensive hypothermia has produced no changes,[5,6] or at best minimal increases[7] in serum TSH. More prolonged exposure to cold generally results in maintenance of the total T4 (TT4) and free T4 (fT4) levels with maintenance of a normal or decreased total T3 (TT3) and free T3 (fT3) levels. [7a,7b] *,* however, others have shown prolonged arctic residence leads the increase in TSH to be associates with an increase in, thyroglobulin and T3..[7c] These alterations may be partly the consequence of a direct effect of temperature on the rate and pathways of

thyroid hormone metabolism with more rapid production and clearance of T3. Altered kinetics have been demonstrated in humans [7d], but have been more thoroughly studied in animals.[8,9,9a,9b] It has been more difficult to show a clear seasonal variation in serum hormone concentration. However, the variation demonstrated in several studies[10,11] has been that T4 and T3 values are higher during the colder months.

Cold exposure in animals leads to thyroid gland hyperplasia, enhanced hormonal secretion, degradation, and excretion, accompanied by an increased demand for dietary iodine. All of these effects are presumably due to an increased need for thyroid hormone by peripheral tissues. The prompt activation of pituitary TSH secretion after cold exposure of the rats[12,13] is possibly due in part to a direct effect on the hypothalamus.[14] Exposure to cold has also resulted in augmented TRH production, and serum levels,[16] and blunted responses of TSH to exogenous TRH.[17] These effects have not been reproduced by other laboratories[13,18] although an increase in thyroid hormone secretion has been clearly demonstrated.[6,19,20] In the rat, it is associated with augmented rates of T4 and T3 deiodination, increased conversion of T4 to T3, and enhanced hepatic binding and biliary and fecal clearance of the iodothyronines.[8,9,9a,21,22] Finally, thyroid hormone effects may be enhanced by alterations in co-activators which enhance the activity of thyroid hormone receptors on gene activation.[22a]

Effects of Heat

In general, an increase in ambient temperature has produced effects opposite to those observed during cold exposure, although the effects of heat have not been extensively investigated. As indicated above, thyroid hormone levels in serum tend to be lower during the summer months. A decrease in the serum T3 concentration, with reciprocal changes in the levels of rT3, have been observed in normal subjects acutely exposed to heat and during febrile illnesses.[23,24] In the latter condition, the contribution of the rise in body temperature relative to other effects of systemic illness cannot be dissociated. A decrease in the elevated serum TSH level associated with primary hypothyroidism has been induced by increases in body temperature.[25]

High Altitude and Anoxia

Acute elevations in serum T4 and T3 concentrations occur in humans during the early period of exposure to high altitude.[26] Increases in the rate of T4 degradation and thyroidal RAIU have also been reported.[27,28] At very high elevations (5400-6300 m), elevations in T4, fT4, T3, and TSH with a normal fT3 have been reported.[28a] When compared to those residing at sea level, individuals adapted to altitude were noted to have a lower T4 with higher fT4 and fT3 levels and a normal TSH response to TRH.[28b] Moderate, transient increases in oxygen consumption, not a result of sympathetic activation, were found in one study.[28]

The responses of rats exposed to high altitude or anoxia seem to be quite different. Thyroidal iodinative activity and T4 formation are diminished.[29-31] The partial reversal of these changes by the administration of TSH led the authors of these studies to conclude that the primary effect is probably diminished TSH secretion.

Alterations in Light

Pinealectomy induces a moderate increase in thyroid weight,[32] and continuous light exposure[33] increases the T4 secretion rate of rats by about 20%. In squirrels, continuous darkness produces a decrease in thyroid weight and T4 levels[33a], but this effect is blocked by pinealectomy.[33a] These studies suggest that melatonin has an inhibitory effect on thyroid gland function.[33a,34] A nocturnal increase in Type II deiodinase activity Is blocked by exposure to continuous light.[34a] Although the retinas of rat pups reared in total darkness are totally devoid of TRH, the content of TRH in the hypothalamus remains unaltered.[35] The diurnal variation in hypothalamic TRH content, reflecting both rhythmic synthesis and secretion, is, however, blunted in the absence of cyclical light changes. Little is known about the effect of light on the thyroid in humans. The normal TSH rhythm can be reset by a pulse of light.[35a]

Nutrition

Since thyroid hormone plays a central role in the regulation of total body metabolism, it is not surprising that nutritional factors may profoundly alter the regulation, supply, and disposal of this thermogenic hormone. Although many dietary changes can affect the thyroid economy, the most striking and important effects are related to alterations in total caloric intake and the supply of iodine. The changes associated with caloric deprivation appear homeostatic in nature producing alterations in thyroid hormones which would conserve energy through a reduction in catabolic expenditure. The changes observed with a deficiency or excess of iodine supply generally serve to maintain an adequate synthesis and supply of thyroid hormone, principally through modifications in thyroidal iodide accumulation and binding.

Starvation and Fasting

Multiple alterations in thyroid hormone regulation and metabolism have been noted during caloric restriction. The most dramatic effect is a decrease in the serum TT3 within 24-48 hours of the initiation of fasting.[36-40b] Because changes in the free T3 fraction are usually small, the absolute concentration

of FT3 is also reduced, clearly into the hypothyroid range The marked reduction in serum T3 is caused by a reduction in its generation from T4 rather than by an acceleration in its metabolic clearance rate.[41,42] The decline in T3 concentration is accompanied by a concomitant and reciprocal change in the concentration of total and free rT3. The increase in the serum rT3 concentration tends to begin later and to return to normal at the time serum T3 is being maintained at a low level with continuous calorie deprivation.[38,39] Little change occurs in the concentrations of TT4 and FT4 and the production and metabolic clearance rates of T4.[38,39,41,42] When small changes have been observed, they were generally in the direction of an increase in the FT4 concentration. They are attributed to decreased concentration of the carrier proteins in serum, as well as to their diminished association with the hormone caused by the inhibitory effect of free fatty acids (FFA) the level of which increases during fasting.[40,43]

Decreased outer ring monodeiodination (5'-deiodinase activity) would explain both the decreased generation of T3 from T4 and the excess accumulation of rT3. This hypothesis seems to be fully supported by in vitro studies using liver tissue from fasted fats.[44] It is further supported by the finding of increased generation and serum concentration of 3',5'-T_2 and 3'-T_1 and decreased 3,5-T_2 and 3,3'-T2.[44-47] However, a less important increase in the monodeiodination of the inner ring of T4 (5-deiodination)[42] explains the temporal dissociation of changes in serum T3 and rT3 concentration. A decrease in plasma T3 after fasting with an increase in hepatic type III deiodinase activity and mRNA has also been noted in chickens.[47a] An increase in the nondeiodinative pathway of T4 degradation with the formation of Tetrac has been also reported.[48]

Considerable controversy remains regarding the mechanisms responsible for the observed changes in the rates of the deiodinative pathways of iodothyronines. Decreased generation of nonprotein sulfhydryls (NP-SH) as a cause of the reduction in 5'-deiodinase activity was suggested on the basis of the observed enhancement in enzyme activity by the in vitro addition of dithiothreitol. Reduced glutathione and NADPH had a similar effect.[49] Although Chopra's[50] direct measurements of NP-SH in tissue during fasting seemed to confirm this hypothesis, the precise mechanism is likely more complex. Decreased tissue NP-SH content does not always correlate with the inhibition of T3 generation, which may be restored by glucose refeeding independently of changes in NP-SH content.[50,51]

Composition of the diet rather than reduction in the total calorie intake seems to determine the occurrence of decreased T3 generation in peripheral tissues during food deprivation. The dietary content of carbohydrate appears to be the key ingredient since as little as 50 g glucose reverses toward normal the fast-induced changes in T3 and rT3.[52] Replacement of dietary carbohydrate with fat results in changes typical of starvation.[39,53] Refeeding of protein may partially improve the rate of T3 generation, but the protein may be acting as a source of glucose through gluconeogenesis.[54] Yet, dietary glucose is not the sole agent responsible for all changes in iodothyronine metabolism associated with starvation. For example, the increase in serum rT3 concentration may not be solely dependent on carbohydrate deprivation since a pure protein diet partially restores the level of rT3 but not that of T3[39] (Fig. 5-1). The composition of the antecedent diet also has an effect on the magnitude of the serum T3 fall during fasting.[39,52] It is possible that the cytoplasmic redox state, measured in terms of the lactate/pyruvate ratio rather than glucose itself, regulates the rate of deiodinative pathways of iodothyronines.[55]

The basal serum TSH level during calorie deprivation is either normal or low, the response to TRH is blunted[37-39] and the normal nocturnal rise in TSH is blunted.[40a] These changes are quite surprising given the consistent and profound decrease in serum FT3 levels. Several hypothesis have been proposed to explain this paradox. Because the pituitary is able to continue to respond appropriately during fasting to both suppressive and stimulatory signals,[56] it has been suggested that starvation only "resets" the set point of feedback regulation. A more plausible hypothesis, supported by experimental data,[57,58] proposes that the pituitary is regulated by the intracellular concentration of T3, which may remain unaltered through factors ensuring its continuous local generation during starvation,

whereas a decrease is typically found in other tissues. Further support for this hypothesis comes from a recent study demonstrating that fasting produces a marked increase in hypothalamic Type II Deiodinase mRNA[58a] which would enhance local T3 production. This hypothesis gives credence to the preservation of a closer inverse relationship between serum FT4 and TSH than between FT3 and TSH. Hypothalamic TRH content in starved rats has been reported to be normal,[59] low[60] or even elevated.[60a] The elevation of TRH was accompanied by normal levels of proTRH mRNA and decreased pituitary TSH; it was suggested that this represented decreased TRH release. [60a] In a different study of starved rats, the hypothalamic proTRH mRNA and the TRH content were both decreased,[60b] but these effects were reversed by adrenalectomy suggesting that they were secondary to increased glucocorticoid levels.[60b] Neonatal starvation in rats leads to diminished TRH and TSH production, with resultant hypothyroidism and growth retardation.[61]

Starvation produces a greater than 50% decrease in the maximal binding capacity of T3 to rat liver nuclear receptors within 48 hours.[62] Although accompanied by a diminution of almost equal magnitude in the nuclear T3 content, it is unlikely that the observed change represents an alteration of the receptor content by the hormone as the more profound diminution of nuclear T3 content associated with hypothyroidism does not produce changes in the maximal binding capacity of T3 in rat liver nuclei. The reduction in maximal binding capacity has been demonstrated to coincide with a reduction in the level of the thyroid hormone receptors.[62a] The affinity of the rat liver T3 receptor is not affected by starvation.[62,63] Studies in humans have used circulating mononuclear cells and, probably due to the limited choice of tissue, results have been either equivocal or negative.[64]

Other hormonal and metabolic changes during fasting may account for the observed alterations in the regulation and metabolism of thyroid hormones. Among them are the increase in plasma cortisol and suppression of adrenergic stimuli.[65] Both changes are known to induce independently a decrease in the serum T3 concentration by inhibition of T4 to T3 conversion in peripheral tissues (see below). Accordingly, they may be partly responsible for the decrease in T3 neogenesis during starvation. There is likely a highly complex interplay between the changes in thyroid hormone and the many metabolic changes of starvation. In addition to a direct effect of glucose, changes in FFA, ketosis, and the redox state may influence thyroid hormone metabolism, while T3 itself may impact hepatic glucose production.[40b]

Two major issues of theoretical and practical importance remain unresolved - do the observed changes in thyroid function produce some degree of hypothyroidism, and is this state beneficial to the energy-deprived organism? Although the suppressed serum TSH response to TRH suggests that the starving organism does not suffer from a significant deprivation in thyroid hormone, other observations indicate the contrary. The decreased pulse rate, systolic time interval, oxygen consumption, and decrease in activity of some liver enzymes are suggestive of hypothyroidism at the level of peripheral tissues.[66] Furthermore, administration of T3 to restore its serum level to normal during fasting increased the production and excretion of urea and 3-methylhistidine.[56,67] Larger doses of T3, given during fasting, had even more profound effects. These effects included dramatic increased in the excretion of urea and creatine, and increased plasma levels of ketones and FFA indicating an accelerated protein and fat breakdown.[68] Such evidence leaves little doubt that the decrease in T3 generation during calorie deprivation has an energy- and nitrogen-sparing effect. It is tempting to speculate that the result is beneficial in the adaptation to malnutrition through reduction in metabolic expenditure.

Fasting is not only a useful model for studying the effects of calorie deprivation on thyroid hormone but is also the prototype of the "low T3 syndrome".[69] The latter is produced by a number of chemical agents and drugs, and accompanies a variety of nonthyroidal illnesses. It is possible that malnutrition, concomitant in a number of acute and chronic illnesses, is in part responsible for some of the observed changes in thyroid physiology.

Protein-Calorie Malnutrition (PCM)

As in the case of starvation, PCM is associated with a low serum T3 concentration and increased rT3 levels, probably due to similar changes in iodothyronine monodeiodination. However, important differences exist between the abnormalities in thyroid function observed in PCM and acute calorie deprivation. Most reports indicate important decreases in TBG and TTR concentrations, and there are also indications of hormone binding abnormalities.[70,71] As a consequence, the free concentrations of both T4 and T3 are usually normal.[70,72,72a] Recovery is associated with restoration of the level of serum thyroid hormones and binding proteins. Despite an accelerated turnover time, the absolute amount of extrathyroidal T4 disposed each day is reduced. Refeeding restores the T4 kinetics to normal.[70] The thyroidal RAIU is reduced due to a defect in the iodine-concentrating mechanism.[73] The most striking difference between starvation and PCM is the finding the latter of an exaggerated and sustained TSH response to TRH, with basal TSH levels either elevated or normal.[70,72,72a,72b,74]

The experimental model of protein malnutrition in the rat yielded different results from those observed in humans. Serum T4 and T3 levels were found to be both elevated.[75] However, in the lamb, as in humans, chronic malnutrition leads to a lower rate of T4 utilization.[76]

Overfeeding and Obesity

Overfeeding produces an increase in the serum T3 concentration as a result of an increased conversion of T4 to T3. It is particularly marked when the excess calories are given in the form of carbohydrates.[77] Thus, it appears that the effect of overnutrition on iodothyronine metabolism is the opposite of that of starvation. This finding gives further credence to the speculation that changes in thyroid hormone may serve to modulate the homeostasis of energy expenditure.

Although it has been reported that serum T3 concentrations correlate with body weight,[78] it appears that this phenomenon reflects the effect of an increase in caloric intake on T3 production. Most studies find that obese subjects have normal thyroid function and hormone metabolism.[79] Furthermore, no abnormalities in the hypothalamic-pituitary-thyroid axis have been demonstrated in obese subjects.

Minerals

Iodine. Of the many minerals that may affect thyroid function, iodine is the most important. It is an essential substrate for thyroid hormone synthesis and also interacts with the function of the thyroid gland at several levels.

Acute administration of increasing doses of iodide enhances total hormone synthesis until a critical level of intrathyroidal iodide is reached. Beyond this level, iodide organification and hormone synthesis are blocked (the acute Wolff-Chaikoff block). Chronic or repeated administration of moderate to large doses of iodine causes a decrease in iodide transport resulting in a decrease in its intrathyroidal concentration. The latter relieves the Wolff-Chaikoff block and is known as the *escape* or *adaptation phenomenon.* Although the exact mechanisms of the block and escape remain unknown, they appear to be autoregulatory in nature since they are independent of pituitary TSH secretion. Iodoloactones may play a role in the induction of the Wolff-Chaikoff block.[80] One mechanism through which iodide acts is via desensitization of the thyroid gland to TSH. In TSH stimulated glands, iodine rapidly reduces the level of the mRNA for thyroid peroxidase (TPO) and the Na/I symporter (NIS) but not for thyroglobulin (Tg) or the TSH receptor (TSHr).[80a] Iodine also antagonizes TSH stimulated thyrocyte proliferation.[80a] In FRTL-5 cells, iodine blocks the TSH stimulation of Tg synthesis but does not alter the level of the Tg mRNA.[80b] These actions occur without a change in TSH receptor number, and may, in part, be via an action on adenylyl cyclase.[80c] More detailed description is provided in Chapter 2.

Another effect of large doses of iodine, apparently independent of TSH and hormone synthesis, is the prompt inhibition of hormone release. It has been exploited to achieve rapid amelioration of thyrotoxicosis in Graves' disease and toxic nodular goiters (see Chapters 11 and 13). In normal persons, the inhibitory effect of large doses of iodine on thyroid hormone release produces a transient

decrease in the serum concentration of T4 and T3. It causes, in turn, a compensatory increase in serum TSH, which stimulates hormone secretion and thus counteracts the effect of iodine.[81,82] The mechanisms of thyroidal autoregulation are believed to serve the purpose of accommodating wide and rapid fluctuations in iodine supply.

The most intriguing effects of iodine are the involution of hyperplasia and the decrease in vascularity that occur when the ion is administered to patients with diffuse toxic goiter. Iodine may be able to induce apoptosis in thyroid cells.[82a,82b] Under different circumstances, iodide may intensify the hyperplasia and produce a goiter (Chapter 20).

Iodine deficiency used to be the leading cause of goiter in the world and still remains so in certain regions. When severe, it can cause hypothyroidism and cretinism, described in detail in Chapter 20 . In the United States and the rest of the developed world, untoward effects from excess iodine supplementation or the use of iodine-containing compounds are more common than problems related to iodine deficiency.

Excess iodine can be responsible for the development of goiter, hypothyroidism, and thyrotoxicosis. However, it should be emphasized that these complications usually occur in persons with underlying defects of thyroid function who are unable to utilize the normal adaptive mechanisms. Iodide-induced goiter (iodide goiter), without or with hypothyroidism (iodide myxedema), is encountered with greater frequency in patients with Hashimoto's thyroiditis or previously treated Graves' disease.[83,84] Other predisposed persons include those who have undergone partial thyroid gland resection, patients with defects of hormonogenesis, and some with cystic fibrosis.[85] Drugs such as phenazone,[86,87] lithium,[88] sulfadiazine,[89] and cycloheximide[90] may act synergistically with iodide to induce goiter and/or hypothyroidism.

More rarely, ingestion of excess iodide may cause thyrotoxicosis (iodide-induced thyrotoxicosis or Jodbasedow).[90a] This was initially observed with the introduction of iodine prophylaxis in areas of endemic iodine deficiency.[91,92] It has also been observed after the administration of iodide in excess to patients with nodular thyroid disease residing in areas of moderate iodine deficiency or even iodine sufficiency.[93,94] Although the exact mechanism of induction of thyrotoxicosis remains obscure, it may be related to the stimulation of increased thyroid hormone synthesis in areas of the gland with autonomous nodular activity.

Ingestion of excess iodide by a gravid woman may cause an iodide goiter in the fetus, and if the gland is large enough it may result in asphyxia during the postnatal period (Chapter 20). Consumption of Kombu, the iodine-rich seaweed, is responsible for the occurrence of endemic goiter in the Japanese island of Hokkaido.[95] It has also been suggested that the increase in dietary iodine content in the United States during the last three decades is responsible for the higher recurrence rate of thyrotoxicosis in patients previously treated with antithyroid drugs.[96]

Calcium. Calcium is said to be goitrogenic when in the diet in excess. Administration of 2 g calcium per day was associated with decreased iodide clearance by the thyroid.[97] The action is unknown, but it may in some way make overt a borderline dietary iodine deficiency. Calcium also acutely and chronically reduces the absorption of thyroxine.[97a, 97b]

Nitrate. Nitrate in the diet (0.3 - 0.9%) can interfere with ^{131}I uptake in the thyroid of rats and sheep.[98] This concentration is found in some types of hay and in silages.

Bromine. Bromine is concentrated by the thyroid and interferes with the thyroidal ^{131}I uptake in animals[99,99a] and humans, possibly by competitive inhibition of iodide transport into the gland. Bromine can also induce alterations in cellular architecture, blood supply and can lead to a reduction in T4 and T3 levels.[99b]

Rubidium. Rubidium is goitrogenic in rats.[100] However, the mechanism of action is unknown.

Fluorine. Fluorine is not concentrated by the thyroid but has a mild antithyroid effect, possibly by inhibiting the iodide transport process.[101] In large amounts, it is goitrogenic in animals. The amounts of fluorine consumed in areas with endemic fluorosis are not sufficient to interfere with thyroid function or to produce goiter.[102,103] However, other data suggest that dietary fluorine may exacerbate an iodine deficiency and thus modulate the distribution of goiter in areas with low iodine intake.[104]

Cobalt. Cobalt inhibits iodide binding by the thyroid.[105] The mechanism is unknown. Cobalt deficiency is associated with a reduction in type I monodeiodinase activity and a fall in T3[105a] while cobalt excess may produce goiter and decreased thyroid hormone production. [105b] It is sufficiently active to have been used in the treatment of thyrotoxicosis.[106]

Cadmium. Administration of cadmium to rats or mice decreases serum levels of T4 and T3. [106a,106b] It also decrease the activity of hepatic Type I - 5'Deiodinase.[106a,106c]

Lithium Ion. Lithium ion is goitrogenic when used in the treatment of manic-depressive psychosis and can induce myxedema.[107] Experimentally, lithium increases thyroid weight and slows thyroid iodine release.[108] When lithium carbonate was given to human subjects in doses of 900 mg four times daily, there was a significant decrease in the rate of release of thyroidal iodine in euthyroid and hyperthyroid subjects.[109] Lithium also decreases the rate of degradation of T4 in both hyperthyroid and euthyroid subjects.[110] Inhibition of thyroid hormone release may be the dominant effect of the ion.[110a] Therefore, the decrease in serum T3 concentration is greater in hyperthyroid patients, and changes in the rT3 level, if any, are minimal.[111-113]

A number of mechanisms have been suggested for the effects of lithium. One well-documented phenomenon is a potentiation of an iodide-induced block of binding and hormone release,[88,114] perhaps because lithium is concentrated by the thyroid[115] and increases the intrathyroidal iodide concentration[109,111] (Fig. 5-2). Although it has been shown that lithium inhibits the adenylate cyclase activity in the thyroid gland as well as in other tissues,[116] it also blocks the cAMP-mediated translocation of thyroid hormone. The latter effect, which is probably responsible for the inhibition of hormone release, appears to be due to the stabilization of thyroid microtubules promoted by lithium.[117] In rat brain, lithium administration decreased both the levels of the Type II 5'Deiodinase and the Type III 5 Deiodinase.[117a] In the rat, lithium may also lead to an alteration in the distribution of thyroid hormone receptors with the alpha 1 isoform being increased in the cortex and decreased in the hypothalamus while the beta isoform was also decreaseed in the hypothalamus. [117b]

An exaggerated response of TSH to TRH may be seen in a majority of lithium treated patients[110a] but an elevated basal TSH is usually absent. An increase in the basal serum TSH concentration and its response to TRH most likely represents an early manifestation of hypothyroidism rather than a direct effect of lithium on the hypothalamic-pituitary axis.[118] The prevalence of goiter has been reported to be as high as 60%.[110a] Based on studies in FRTL-5 cells, lithium may have direct mitogenic effects on the thyroid that are independent of TSH and cAMP. [110b] The occurrence of hypothyroidism during lithium therapy occurs in 10-40% of lithium treated patients and is far more frequent in women than men.[110a,118a, 118b,118c]

Although much less frequent, lithium therapy has been associated with the development of thyrotoxicosis.[110a] Lithium is also reported to produce exophthalamos during chronic therapy; the condition regresses when treatment is stopped. The phenomenon is a protrusion of the globe but does not involve the other changes of infiltrative ophthalmopathy of Graves' disease.[118,119]

Selenium. Selenium is a component of the enzymes glutathione peroxidase (GSH-Px) and superoxide dismutase, both enzymes responsible for protection against free radicals. In addition, Type I 5'Deiodinase also contains selenium.[119a] [119c] Thus, a deficiency of selenium could predispose the thyroid to oxidative injury and lead to decreased peripheral T3 production. In the elderly, reduced selenium levels have been associated with a decreased T3/T4 ratio.[119b] It has been postulated that the combined deficiency of iodine and selenium in Zaire results in myxedematous rather than neurologic cretinism because the decrease in peripheral conversion to T3 results in greater delivery of T4 into the neonatal developing brain.[119c] In rats, selenium deficiency led to a decrease in renal but not hepatic Type I 5' Deiodinase activity and serum T3 levels were unaffected.[119d] Selenium deficiency led to decrease GSH-Px activity in the liver, kidney and rbc's but not the thyroid.[119d] Serum T4 was normal when both dietary iodine and selenium were both deficient, but was reduced when either was deficient alone.[119d] In other studies, brain GSH-Px and Type I deiodinase activity were normal in the presence of iodine or selenium deficiency while brain Type II Deiodinase activity was increased by iodine deficiency and unaffected by selenium deficiency.[119e] In contrast in brown adipose tissue (BAT), both selenium and iodine deficiency led to decreased deiodinase activity and decreased production of the uncoupling protein.[119e]

Treatment of goitrous children with combined seleium and iodine deficiency leads to a reduction in serum TSH and goiter size.[119f] The response, however, was correlated with the selenium level with both the goiter and TSH responses being correlated with the baseline selenium level. [119f] In an epidemeological study in China, low selenium levels were assocated with an increased ididence of goiter, sub-clinical and overt hypothryoidism and thyroiditis. [119g]

Physical and Emotional Stress

Perhaps the most dramatic study of emotional stress is that reported by Kracht,[120] who found that stress provoked thyrotoxicosis in wild rabbits. Although some stress models may prompt secretion of thyroid hormone in animals,[120,121] this effect is unlikely to occur in humans, at least for a sustained period of time. The stress-induced increase in adrenocortical activity tends not only to suppress TSH release but also to inhibit T3 production. A major problem in the analysis of available date is the difficulty in separating effects produced by non-specific stress from the effects caused by the agents used to induce the stress. Many of the changes in thyroid function described in this chapter under the headings starvation, temperature, altitude and anoxia may be due, in part, to stress.

Surgery

Surgery has been used as a means to study the effect of stress on thyroid physiology in animals.[122] Studies in humans have been prompted by the suspicion that thyroid hormone may mediate the postoperative metabolic changes leading to increased oxygen consumption and protein wastage. Some discrepancies in available data stem from lack of uniformity in the groups of patients studied in terms of preoperative state or disease, type of surgery, types of anesthetic agents and other drugs used, and the postoperative course, including nutrition and the period of recovery.

The most striking change in thyroid function is a decrease in the serum TT3 and FT3 concentrations shortly after surgery; rT3 concentrations are elevated in the postoperative period.[123,124] The combined findings suggest a diversion in the normal deiodinative pathways of T4. FT4 levels may also be depressed in the postoperative period, but to a lesser degree.[124] The TTR but not the TBG level is sharply reduced.[125] This clear reduction in the concentration of the active forms of thyroid hormone during the postoperative period is preceded by a small, short-term increase in FT4 and FT3 concentrations during surgery.[123,124] The magnitude of the subsequent reduction in T3 level appears to correlate with the severity of trauma and the morbidity during the postoperative course.[123] The serum TSH concentration also tends to diminish,[124] except during surgery performed in children under the conditions of hypothermia.[2]

Because surgical trauma produces a prompt elevation in plasma cortisol levels and food intake is curtailed during the pre-, intra-, and postoperative periods, the possibility that glucocorticoids and starvation are the principal contributors to the observed changes in thyroid function has been given strong consideration. However, Brandt et al.[126] showed equally profound diminution in the serum T3 concentration when surgery was carried out with epidural anesthesia, which abolishes the plasma cortisol surge. Similarly, the almost routine use of glucose infusion should have been able to prevent the changes in serum T3 and rT3 levels if starvation played a major role in producing the changes observed during surgery.

Acute Mental Stress

Data on the effect of emotional stress on thyroid function in humans are principally derived from studies in patients with psychiatric disturbances. Thus, even if only patients with acute psychiatric decompensation are considered, the results are colored by the nature of the mental illness, its antecedent history, and the use of drugs. An early suggestion of enhanced hormonal secretion came from the observation of elevated protein-bound iodine (PBI) levels in the serum of psychiatric patients presumably under emotional stress and in medical students in the course of examinations.[127] In more recent studies, elevations of the FT4I have been consistently found during admission of acute psychiatric patients. The incidence ranged from 7 to 18%.[128-130] In one study, an equal number of patients (9%) had a low FT4I.[128] In most instances, values became normal with time and treatment of the psychiatric illness. The TSH response to TRH is blunted or even absent in most psychiatric patients with elevated FT4I.[130] Significant abnormalities in the serum T3 concentration are rare.

CHEMICALS AND DRUGS

Goitrogens

A number of compounds have the ability to inhibit thyroid hormone synthesis (Fig.5-3). Irrespective of their mechanism of action, they are collectively called *goitrogens.* As a result of a decrease in serum thyroid hormone levels, TSH secretion is enhanced, causing goiter formation. Some goitrogens occur naturally in food, and others are in drugs with goitrogenic side effects. The least toxic and those possessing the highest thyroid-inhibiting activity are used in the treatment of hyperthyroidism.

Dietary Goitrogens

The discovery of natural and synthetic substances that impair the synthesis of thyroid hormone are landmarks in the history of pharmacology.[131] These substances are discussed in more detail in Chapter 20. Although iodide deficiency is, without doubt, the major cause of endemic goiter and cretinism throughout the world, dietary goitrogens may play a contributing role in some endemics, and may possibly be the dominant factor in certain areas. The dietary goitrogens fall into several categories, more than one of which may occur in the same food.

Certain foods contain cyanogenic glucosides,[132] compounds that, upon hydrolysis by glucosidase, release free cyanide. These foods include almond seeds and such important dietary items as cassava, sorghum, maize, and millet. Cassava contains enough cyanogenic glucoside to be lethal if large quantities are consumed raw. Ordinarily, the root is extensively soaked, then dried and powdered. Most of the cyanide is lost in this process; that left in the root is liberated after ingestion and converted to SCN^-. Chronic poisoning due to cassava is responsible for a tropical neuropathy in Nigeria[133] and Tanzania, and is suspected of being a contributing cause of goiter in Central Africa.[134,135]

Other important classes of antithyroid compounds arise from hydrolysis of the thioglucosides.[132,136,137] These compounds are metabolized in the body to goitrin or thiocyanates and isothiocyanates, and ultimately to other sulfur containing compounds, or are excreted as such. They are important in the goitrogenic activity of seeds of plants of the genus *Brassica* and the cruciferae, compositae, and unbelliferae. Among the plants containing these compounds are cabbage, kale,

brussel sprouts, cauliflower, kohlrabi, turnip, rutabaga, mustard, and horseradish. Myxedema was reported in a woman without previous thyroid disease who consumed extremely large amounts of raw bok choy. [137b] Cattle may ingest these goitrogens and pass them to humans through milk, as observed in Australia,[138] Finland,[139,140] and England.[141] . The isothiocynate, cheiroline, occurs in the leaves of choumoellier and may be related to a focal area of endemic goiter in Australia. The goitrogen is thought to be transmitted from forage to cows, to milk, and finally to children. Although there is considerable circumstantial evidence relating these compounds to endemic goiter, it has been difficult to prove their role with certainty.

Thiocyanate is a well-known inhibitor of iodide trapping when in high concentration in blood. The blood levels obtained by ingestion of dietary goitrogens are rarely of this degree. Inhibition of iodide trapping, and thyroid peroxidase activity, and augmentation of urinary iodide loss, as demonstrated by Delange and Ermans and co-workers, all may play a role in the goitrogenic activity.[132,134,135] Thiocyanate may also reduce the iodine content of breast milk or animal milk and thus indirectly impact the thyroid function of young children in areas of marginal iodine sufficiency.[141a] A study in Thailand found an association between thiocyanate levels and TSH in pregnant women with low iodine excretion. [141b]

Astwood et al. and Greer[142,143] found that turnips contain progoitrin, which is a mustard oil thioglycoside. It undergoes rearrangement by enzymes in human enteric bacteria, or in the turnip, to be converted to goitrin, an active goitrogenic thioglycoside, L-5-vinyl-2-thio-oxazolidone.[144,145] Goitrin inhibits oxidation of iodine and its binding to thyroid protein in the same way as do the thiocarbamides.

Several endemics of goiter have been attributed to dietary goitrogens, usually acting together with iodine deficiency. Goitrin is apparently present in cow's milk in Finland.[146] In the Pedgregoso region of Chile, pine nuts of the tree *Araucaria americana* are made into a flour and consumed in large amounts, and may be related to endemic goiter.[147,148] In the Cauca river valley of Colombia, sulfur-containing compounds found in the water supply, derived from sedimentary rocks containing a large amount of organic matter, are believed to be responsible for endemic goiter.[149] At least, extracts from these waters are goitrogenic in rats. Pearl millet has been reported to cause goiter development in goats. [149a]

Other mechanisms may also contribute to dietary goitrogenicity. Thus, diets high in soybean components or other materials increasing fecal bulk may cause excess fecal loss of T4 and increase the need for this hormone.[150-153] These diets are low in iodine content, and soybean has been thought but not proven to contain a goitrogen.

The goitrogens, by blocking hormone synthesis, deplete the thyroid of iodide; this reduction itself increases the sensitivity of the gland to TSH.[154] This sensitivity, in turn, further promotes goitrogenicity.

Antithyroid Drugs

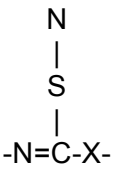
According to their principal mode of action on thyroidal iodine metabolism, antithyroid drugs are divided into two categories: (1) the monovalent anions, which inhibit iodide transport into the thyroid gland, and (2) a large number of compounds that act through inhibition of thyroidal iodide binding and iodotyrosine coupling. The most important representatives of this latter category of compounds are the group of thionamides. The effect of the drugs in the first category is counteracted by exposure to excess iodine, whereas iodine has no inhibition, and at times even potentiates, the action of drugs in the second category. Other drugs inhibit thyroid hormone secretion or act through yet unknown mechanism. A list of these agents is provided in Table 5-1.

Monovalent Anions. Certain monovalent anions (SCN^-, $Cl0_4^-$, NO_3^-) inhibit transport of iodide into the thyroid gland and thereby depress iodide uptake and hormone formation.[164-166] Thiocyanate stimulates efflux of iodide from the thyroid as well,[167] and also inhibits iodide binding and probably coupling.[168,169] A large number of complex anions, such as monofluorosulfonate, difluorophosphate, and

fluoroborate,[170] inhibit iodide transport. Of these, fluoroborate,[171] and perchlorate,[172] are concentrated by the thyroid gland. These ions have a molecular volume and charge similar to those of iodide, and may compete with iodide for transport.[170,171] Perchlorate is sufficiently active to be useful clinically.[173] Perchlorate and thiocyanate also displace T4 from thyroid hormone-binding serum proteins in vivo and in vitro and cause a transient elevation of free T4.[174] In contrast to the pharmacologic effects of perchlorate, concerns have been raised about the potential health effects of environmental perchlorate exposure, especially in municipal water supplies. Several studies have been unable to detect an increase in hypothyroidism [174a. 174b], congenital hypothyroidism [174c], or thyroid cancer [174d] in exposed populations, but a study in Thailand found an association bwteen perchlorate levels and TSH in pregnant women. [141b]

Thionamides. The thionamide and thiourylene drugs do not prevent transport of iodide into the thyroid gland, but rather impair covalent binding of iodide to TG.[175-177] They may be competitive substrates for thyroid iodide peroxidase, preventing the peroxidation of iodide by this enzyme. In small doses, the thiocarbamides inhibit formation of iodothyronines from iodotyrosyl precursors. When slightly larger amounts are present, iodination of MIT and tyrosine is prevented.[177,178] Minute amounts (10^{-8} M) have, paradoxically, a stimulatory effect on iodination in thyroid slices.[179]

The basic structure necessary for the antithyroid action of these drugs is



where X may be C, N, or O[180,181] (Fig. 5-3). The thiocarbamides are metabolized in the thyroid gland by transsulfuration.[182] The enzyme responsible may also be involved in the iodide peroxidase enzyme system.[183] Glands under TSH stimulation metabolize the antithyroid drugs at an accelerated rate, as has been shown for thiourea.[184]

Iodide is released more rapidly from a gland blocked by PTU than from one blocked by perchlorate.[165,185] This action occurs presumably because PTU prevents the utilization of all iodide available to the gland (transported from the blood or formed in the gland by deiodination of iodotyrosines), whereas potassium perchlorate prevents uptake of iodide but does not inhibit reutilization of iodide derived from within the gland. T4 disappears from the PTU-blocked rat thyroid at a faster rate than do iodotyrosines.[185]

In addition to the effects on the thyroid gland, PTU (and, to a much lesser extent, methimazole) partially inhibits the peripheral deiodination of T4[186-191] and its hormonal action.[188,192-194] PTU acts directly on body tissues to inhibit the normal formation of T3 from T4.[191,195] Coincidentally, fecal excretion of T4 increases.[186] In order to inhibit goiter induced by antithyroid drugs in rats, one must maintain the T4 concentration in blood at a higher level that is normal for the species.[188,192] Presumably, inhibition of T4 monodeiodination by the antithyroid drug leads to a buildup of T4 in blood and diminishes the availability of T3 in the tissues.[191] Higher doses of T4 or higher blood levels may be sufficient to push the reaction toward T3 and allow formation of quantities sufficient to prevent goiter.

Metabolism of the antithyroid drugs has been observed after administration of ^{35}S-labeled drugs. Methimazole is rapidly absorbed from the gastrointestinal tract in humans. It reaches a peak plasma level about an hour after administration, and then declines gradually to near zero levels at 24 hours. These drugs are accumulated and degraded in the thyroid, since they are substrates of the peroxidase.[196,197] Carbimazole is accumulated as its metabolic product, methimazole. The concentration ratio between thyroid and plasma for unmetabolized methimazole in rats may approach 25, eight hours after administration of the drug. The metabolic products derived from the drug are excreted in the urine, largely during the first day.

Other Goitrogenic Compounds

A number of other drugs, including the aminoheterocyclic compounds and substituted phenols, act as goitrogens principally by impairing TG iodination (Fig. 5-3). They are in general far less potent in their goitrogenic effect than the thionamides. None are used therapeutically as antithyroid drugs; rather, goitrogenesis is an undesirable side effect of their use. Some the compounds have multiple effects and thus influence thyroid physiology at various levels. These compounds are individually discussed in greater detail. A comprehensive list is provided in Table 5-1.

Table 5-1 Agents Inhibiting Thyroid Hormone Synthesis and Secretion

Substance	*Common Use*
Block iodide transport into the thyroid gland	
Monovalent anions (SCN^-, $Cl0_4^-$, $N0_3^-$)[a]	Not in current use; $Cl0_4^-$ test agent
Complex anions (monofluorosulfonate, difluorophosphate, fluoroborate)[a]	
Minerals (bromine, fluorine)	In diet
Lithium[a]	Treatment of manic-depressive psychosis
Ethionamide	Antituberculosis drug
Impair TG iodination and iodotyrosine coupling	
Thionamides and thiourylenes, (PTU, methimazole, carbimazole)[a]	Antithyroid drugs
Sulfonamides (acetazolamide, sulfadiazine sulfisoxazole)[a]	Diuretic, bacteriostatic
Sulfonylureas (carbutamide, tolbutamide, metahexamide, ?chloropropamide)[a]	Hypoglycemic agents
Salicylamides (*p*-aminosalicylic acid, *p*-aminobenzoic acid)[a]	Antituberculosis drugs
Resorcinol]	Cutaneous antiseptic
Amphenone	Anticonvulsive
Aminoglutethimide	Antiadrenal agent
Thiocyanate[a]	No current use; in diet
Antipyrine (phenazone)[a]	Antiasthmatic
Aminotriazole	"Cranberry poison"
Amphenidone	Tranquilizer
2,3-Dimercaptopropanol (BAL)	Chelating agent
Ketoconozole	Antifungal agent
Inhibitors of thyroid hormone secretion	
Amiodarone [a]	Antianginal and antiarrhythmic agent

Iodide (in large doses)[a]	Antiseptic, expectorant, and others
Lithium[a]	See above
Thryoiditis	
Amiodarone [a]	Antianginal and antiarrhythmic agent
Interleukin II [a]	Chemotherapeutic agent
γ-Interferon [a]	Antiviral and cancer therapy
Sunitinib [a]	Cancer therapy
Sorafenib [a]	Cancer therapy
Ipilmumab [a]	Cancer therapy
Pembrolizumab [a]	Cancer therapy
Nivolumab [a]	Cancer therapy
Mechanism unknown	
p-bromdylamine maleate [a]	Antihistaminic
Phenylbutazone [a]	Antiinflammatory agent
Minerals (calcium, rubidium, cobalt)[a]	-----
Thalidomide[396]	Cancer therapy

[a]References given in the text

Sulfonamides. Sulfonamides, particularly those containing an aminobenzene grouping, have antithyroid activity. Acetazoleamide (Diamox), the diuretic agent, has a strong effect on animals and humans.[198,199] Its action, prevention of intrathyroidal iodide binding, is not related to carbonic anhydrase inhibition. Sulfadiazine and sulfisoxazole have a similar action, probably through a synergistic effect on iodide.[89]

Sulfonylureas. Sulfonylureas, derivatives of sulfonamides and used as hypoglycemic-antidiabetic agents, also inhibit the synthesis of thyroid hormone. They include carbutamide, tolbutamide, methahexamide, and possibly chlorpropamide, but not the phenylethyl biguanide (Fig. 5-3). They impair thyroidal RAIU and cause goiter in the rat.[200,201] Carbutamide is much more potent than tolbutamide. Carbutamide, 2 g/day (but not 1 g/day), may reduce the thyroidal RAIU in humans to 20% of control values, but the uptake gradually rises as treatment is continued and is normal after 20 weeks. From 1 to 2 g tolbutamide per day does not affect RAIU in humans.[202] Thus, in the usual dose range, tolbutamide will not depress thyroid function.

Chlorpropamide in large doses (3-7 g) depresses the RAIU in humans; the common therapeutic doses (up to 1 g daily) usually have no effect on serum T4.[203] A mild antithyroid action is often reflected in a rise in RAIU, which may be found after the agents are withdrawn.

These drugs inhibit hormone synthesis by inhibition of iodide binding. In most instances, the pituitary compensates for the effect and maintains a euthyroid state by increased synthesis of TSH. Nevertheless, hypothyroidism is said to be more common in diabetic patients on sulfonylureas than in patients treated by other means.[204]

Sulfonylureas also block binding of T4 to the carrier proteins in serum and thus depress the T4 concentrations.[205] This effect is most pronounced after intravenous administration.

Polychlorinated Biphenyls Animal studies have suggested that polchlorinated bihenyls (PCBs) may reduce thyroid hormone levels by decreasing synthesis, increasing biliary excretion of conjugated metabolites and displacing T4 from binding proteins. [205a] A review of studies in humans, did not find significant or consistent changes. [205a]

Effects of Miscellaneous Compounds and Drugs

General Mechanisms of Action

A large number of substances may affect thyroid gland function and thyroid hormone metabolism and action. The list continues to grow with the introduction of new diagnostic agents, drugs, and food additives. Drugs affect the transport, metabolism, action and excretion of T4 and its derivatives as well as regulation at all levels of the hypothalamic-pituitary-thyroid axis. Some drugs may induce hypothyroidism or thyrotoxicosis, and if autoimmune mechanisms are involved, the thyroid dysfunction may not resolve with discontinuance of the drug. Some compounds may not have any direct effect on thyroid hormone economy or regulation, but have clinical relevance by interfering in specific diagnostic assays.

Compounds are discussed and listed below based on their major mechanisms of action. Many drugs have more than one mechanism of action and the explanation for observed abnormalities is not always known. Results of experiments conducted in animals or in vitro are not always applicable to human pathophysiology. Compounds which alter thyroid hormone secretion are generally goitrogens or anti-thyroid drugs and were discussed in the preceeding section. Selected compounds with significant effects on the thyroid, wide-spread use or that are of particular interest in understanding the mechanism of drug effects are described in greater detail.

Alterations of Thyroid Hormone Transport

Some hormones and drugs may affect thyroid hormone transport in blood by altering the concentration of the binding proteins in serum. Thyroid hormone transport may also be affected by substances that compete with the binding of thyroid hormone to its carrier proteins (Table 5-2). TBG synthesis is increased by estrogens[220-223] and decreased by androgens and anabolic steroids.[223,224] Estrogen's effect to increase TBG is blunted or reversed by tamoxifen and raloxifene.[224a] The most extensively studied compounds that interfere competitively with thyroid hormone binding to the carrier proteins in serum are salicylates, diphenylhydantoin, and heparin.[212,225-231,231a,b] A clinically significant effect of furosemide[211] may only be seen with very high doses and with accumulation with renal failure.

Table 5-2 Compounds that Affect Thyroid Hormone Transport Proteins in Serum

Substance	*Common Use*
Increase TBG concentration	
Estrogens[a]	Ovulatory suppressants, anticancer agents
Heroin and methadone[206]	Opiates (in addicts)

Clofibrate[207]	Hypolipemic agent
5-Fluorouracil[208]	Anticancer agent
Perphenazine[209]	Tranquilizer

Decrease TBG concentration

Androgens and anabolic steroids[a]	Virilizing, anticancer, and anabolic agents
Glucocorticoids[a]	Antiinflammatory, immunosuppressive, and anticancer agents; decrease intracranial pressure
L-Asparaginase[210]	Antileukemic agent
Nicotinic acid[210a ,210b]	Hypolipidemic agent

Interfere with thyroid hormone binding to TBG and/or TTR

Salicylates and salsalate[a]	Antiinflammatory, analgesic, antipyrexic, and antituberculosis agents
Diphenylhydantoin and analogs[a]	Anticonvulsive and antiarrhythmic agents Antianxiety agent
Furosemide[211]	Diuretic
Sulfonylureas[a]	Hypoglycemic agents
Heparin[a]	Anticoagulant
Dinitrophenol[a]	Uncouples oxidative phosphorylation
Free fatty acids[212,213]	--------
o,p'-DDD[214]	Antiadrenal agent
Phenylbutazone[215]	Antiinflammatory agent
Halofenate[216]	Hypolipemic agent
Fenclofenac[217]	Antirheumatic agent
Orphenadrine[218]	Spasmolytic agent
Monovalent anions (SCN^-, $C104^-$)[a]	Antithyroid agents
Thyroid hormone analogs, including dextroisomers[219]	Cholesterol reducing

[a]References given in the text

In general, the effect of increased hormone binding is an increase in the serum concentration of total (bound) T4 and of reduced binding is a decrease in the total (bound) T4, with T3 effected to a lesser extent. There is no significant effect on the absolute concentration of the metabolically active fractions of FT4 and FT3, or usually their free indices (FT4I and FT3I). In the steady state, the quantity of thyroid hormone reaching peripheral tissues and the pathways and amount of hormone degradation remain

unaltered. However, before this steady state is reached, an acute perturbation in the equilibrium between free and bound hormone brings about transient changes in thyroid hormone secretion and degradation. The hypothalamic-pituitary-thyroid axis participates in the reestablishment of the new steady state. For example, as illustrated in Figure 5-4, an abrupt increase in the concentration of TBG shifts the equilibrium between total and bound hormone, causing a decrease in the concentration of free hormone. The consequences are fourfold. First, there is a shift in the exchangeable hormone from tissues to blood. Second, a decreased hormone content in tissues diminishes its absolute degradation rate. Third, a decline in hormone concentration in tissues activates the hypothalamic-pituitary axis, causing an increase in TSH secretion. Fourth, the latter acts on the thyroid gland to step up its hormonal secretion and reestablish an appropriate thyroid hormone/TBG ratio. Thus, a normal thyroid hormone concentration in serum and tissues and hormonal production and disposal rates are reestablished. TSH concentration returns to normal, and a new steady state is maintained at the expense of an increased intravascular pool and a decreased fractional turnover rate and total distribution space of thyroid hormone.[232,233] The reverse sequence of events accompanies an acute decrease in TBG concentration or binding (Fig. 5-4).

Alterations of Thyroid Hormone Metabolism

Agents that may alter the extrathyroidal metabolism of thyroid hormone are listed in Table 5-3. Several drugs with wide use in clinical practice inhibit the conversion of T4 to T3 in peripheral tissues. Glucocorticoids,[239,240] amiodarone,[241,242] and propranolol[243-245] are a few examples. As expected, their most profound effect on thyroid function is a decrease in the serum concentration of T3,[239,241,243] usually with a concomitant increase in the rT3 level.[239,241] An increase in the serum T4 concentration has also been observed on occasion.[241,245] The serum TSH concentration may also occasionally rise,[241] provided the drug does not have a direct inhibitory effect on the hypothalamic-pituitary axis.[246] In the absence of inherent abnormalities in thyroid hormone secretion or in its regulation, TSH levels should return to normal and hypothyroidism should not ensue from the chronic administration of compounds the only effect of which is to interfere partially with T4 monodeiodination.

Other mechanisms by which some compounds affect the extrathyroidal metabolism of thyroid hormone are acceleration of the overall rates of deiodinative and nondeiodinative routes of hormone disposal. Examples of drugs acting principally through the former mechanism are diphenylhydantoin and phenobarbital,[247-249] and via the latter, colestipol[237], ferrous sulfate[238a], aluminum hydroxide[238b] and sucralfate[238c]. Patients receiving these drugs should increase the secretion of hormone from the thyroid gland in order to compensate for the enhanced hormonal loss through degradation or fecal excretion. Thyroid hormone concentration in blood should remain unaltered. However, hypothyroid patients receiving such drugs may require higher doses of exogenous hormone to maintain a eumetabolic state (Chapter 9). In patients on thyroid hormone therapy who are also taking drugs which bind thyroid hormone in the gastrointestinal tract, the administration of the two drugs at different times will markedly reduce or eliminate the effect on thyroid hormone absorption.

Acute increases in serum T4 and FT4 concentration after the injection of insulin or during halothane anesthesia have been attributed to an enhanced release of T4 normally stored in the liver.[250,251]

Table 5-3 Agents that Alter the Extrathyroidal Metabolism of Thyroid Hormone

Substance	*Common Use*
Inhibit conversion of T4 to T3	
PTU[a]	Antithyroid drug

Glucocorticoids (hydrocortisone, prednisone, dexamethasone)[a] Decrease intracranial pressure	Antiinflammatoryand immunosuppressive; decrease intracranial pressure
Propranolol[a]	ß-Adernergic blocker (antiarrhythmic, antihypertensive)
Iodinated contrast agents [ipodate (orgrafin), iopanoic acid (Telepaque)][a]	Radiologic contrast media
Amiodarone[a]	Antianginal and antiarrhythmic agent
Clomipramine[234]	Tricylic antidepressant

Stimulators of hormone degradation or fecal excretion

Diphenylhydantoin[a]	Anticonvulsive and antiarrhythmic agent
Carbamazepine[235]	Anticonvulsant
Phenobarbital[a]	Hypnotic, tranquilizing, and anticonvulsive agent
Cholestyramine[236] and colestipol[237]	Hypolipemic resins
Soybeans[151 152]	Diet
Rifampin[238a]	Antituberculosis drug
Ferrous Sulfate[238]	Iron therapy
Aluminum hydroxide[238b]	Antacid
Sucralfate[238c]	Anti-ulcer therapy
Imatinib [384]	Cancer therapy
Bexarotene [387]	Cancer therapy
Sevelemer [393]	Phosphate Binder
Colesevelam [394]	Hypolipemic resin
Lanthanum Carbonate [394]	Phosphate Binder
Coffee [395]	Diet

[a]References given in the text

Alterations of Thyroid Hormone Regulation

The last two decades have seen a prodigious growth in the list of substances that can be shown to act on the hypothalamic-pituitary axis (Table 5-4). Although many of these compounds are used frequently,

only a few have significant effects on thyroid function via this central mechanism. Furthermore, patients receiving these drugs rarely have any abnormality of serum TSH although the response of TSH to the administration of TRH may be altered. An effect of these drugs may be seen in patients with untreated or partially treated primary hypothyroidism. In patients with an elevated basal level of serum TSH, addition of these drugs may produce a further increase or a significant diminution.

Although the following paragraphs discuss the general mechanisms of action for these compounds, specific mechanisms are not always known. A major problem in interpretation is the variability of experimental designs. These variables include doses, routes of administration, duration and time of treatment, drug combinations, age and sex of subjects, hormonal status at the time of testing, and time of blood sampling. Furthermore, observed responses may be effected by the method of data analysis. For example, results of TSH responses to TRH have been expressed in terms of changes in the absolute value, increments or decrements from the basal level, and percent of the basal value at either the peak and nadir of the response or the integrated area over the duration of the response.

The most potent suppressors of pituitary TSH secretion are thyroid hormone and its analogs. They act on the pituitary gland by blocking TSH secretion through the mechanisms discussed in Chapter 4. Some TSH-inhibiting agents listed in Table 5-4, such as, fenclofenac and salicylates, may act solely by increasing the free thyroid hormone level through interference with its binding to serum proteins. Other agents appear to have a direct inhibitory effect on the pituitary and possibly on the hypothalamus. The most notable is dopamine and its agonists. They have been shown to suppress the basal TSH levels in euthyroid persons[284,285] and in patients with primary hypothyroidism.[267,284-286] More uniformly, they suppress the TSH response to the administration of TRH.[268,285,287,288] In contrast, most dopamine antagonists increase TSH secretion.[150-155] Increases in the basal TSH and in its response to TRH have been observed in euthyroid persons,[252,255] as well as in patients with primary hypothyroidism[250-256] who have been given these drugs. A notable exception to this rule, which casts some doubt on the assumed mechanism of action of dopamine antagonists, is neuroleptic dopamine blocker, pimozide, which has been reported to reduce the elevated serum TSH level in patients with primary hypothyroidism.[289]

Table 5-4 Agents that May Affect TSH Secretion

Substance	*Common Use*
Increase serum TSH concentration and/or its response to TRH	
Iodine (iodide and iodine-containing compounds)[a]	Radiologic contrast media, antiseptic expectorants, antiarrhymic and antianginal agents
Lithium[a]	Treatment of bipolar psychoses
Dopamine receptor blockers (metclopramide,[252,253] domperidone[253 254])	Antiemetic
Dopamine-blocking agent (sulpiride[255])	Tranquilizer
Decarboxylase inhibitor (benserazide[256])	-----
Dopamine-depleting agent	-----

(monoiodotyrosine[253])	
L-Dopa inhibitors (chloropromazine,[257] biperidine,[258] haloperidol[258])	Neuroleptic drugs
Cimetidine (histamine receptor blocker)[259]	Treatment of peptic ulcers
Clomifene (antiestrogen)[260]	Induction of ovulation
Spironolactone[261]	Antihypertensive agent
Amphetamines[262]	Anticongestants and antiappetite

Decrease serum TSH concentration and/or its response to TRH

Thyroid hormones (T4 and T3)	Replacement therapy, antigoitrogenic and anticancer agents
Thyroid hormone analogs (D-T4,[263] 3,3',5-Triac,[264] etiroxate-HCl,[265] 3,5-dimethyl-3-isopropyl-L-thyronine[266])	Cholesterol-lowering and weight reducing agents
Dopaminergic agents (agonists)	
Dopamine[a]	Antihypotensive agent
L-Dopa[a] (dopamine precursor)	Diagnostic and anti-Parkinsonian agent
2-Brom-α-ergocryptine[a]	Antilactation and pituitary tumor suppressive agent
Fusaric acid (inhibitor of dopamine ß-hydroxylase[267])	------
Pyridoxine (coenzyme of dopamine synthesis[268])	Vitamin and antiheuropathic agent
Other dopaminergic agents (perbidil,[269] apomorphine,[269] lisuride[270])	Treatment of cerebrovascular diseases and migraine
Dopamine antagonist (pimozide)[a]	Neuroleptic agent
α-Noradrenergic blockers (phentolamine,[271] thioridazine[272])	Neuroleptic agents
Serotonin antagonists (metergoline,[273] cyroheptadine,[274] methysergide[275])	Antimigraine agents and appetite stimulators
Serotonin agonist (5-hydroxytryptophan[276])	-----
Glucocorticoids[a]	Antiinflammatory, immunosuppressive, and anticancer agents Reduction of intracranial pressure

Acetylsalicylic acid[a]	Antiinflammatory, antipyrexic and analgesic agent
Growth hormone[277 b]	Growth-promoting agent
Somatostatin[278,279]	-----
Octreotide [279a]	Treatment of carcinoids, acromegaly and other secretory tumors
Opiates (morphine,[280] leucine-eukephaline,[281] heroin[282])	Analgesic agents
Clofibrate[283]	Hypolipemic agent
Fenclofenac[216]	Antirheumatic agent
Bexarotene [a]	Cancer therapy
Metformin [392]	Anti-diabetic agent
Ipilmumab [a] (autoimmune hypophysitis)	Cancer therapy
Pembrolizumab [a] (autoimmune hypophysitis)	Cancer therapy
Nivolumab [a] (autoimmune hypophysitis)	Cancer therapy

[a]References given in the text
[b]In hyposomatotrophic dwarfs

Iodine and some iodide-containing organic compounds cause a rapid increase in the basal and TRH-stimulated levels of serum TSH. This effect is undoubtedly due to a decrease in the serum thyroid hormone concentration either by inhibition of hormone synthesis and secretion by the thyroid gland[81,82] or by a selective decrease in the concentration of T3.[290] The latter effect is mediated through the inhibition of T3 generation from T4. A more selective, intrapituitary inhibition of T4 to T3 conversion appears to be responsible for the TSH-stimulating effect of the radiographic contrast agent iopanoic acid[58] and amiodarone. Iodine does not stimulate TSH secretion in patients in whom it has produced hyperthyroidism. [94] A decrease in the free thyroid hormone concentration in serum, albeit minimal in magnitude, may also be responsible for the increase in TSH levels observed during treatment with clomifene.[260]

It has been postulated that some agents may act by modifying the effect of TSH on its target tissue. For example, theophylline may potentiate the action of TSH through its inhibitory effect on phosphodiesterase, which may lead to an increase in the intracellular concentration of cAMP.[291] In fact, the presence of the pituitary is required to demonstrate that methylxanthines augment the goitrogenic effect of a low-iodine diet in the rat.[292] One of the postulated effects of diethyl ether anesthesia in the rat is inhibition of the action of TSH on the thyroid gland,[293] although it has also been reported to induce a transient redistribution of T4 between serum and tissues.[294]

Alterations of Thyroid Hormone Action

A handful of drugs seem to act by blocking some of the peripheral tissue effects of thyroid hormone. Others appear to mimic one or several manifestations of the thyroid hormone effect on tissues. Guanethidine releases catecholamines from tissues.[295] It has a beneficial effect in thyrotoxicosis, including a decrease in BMR, pulse rate, and tremulousness.[296,297] This agent has little effect on the

thyroid gland, but depresses manifestations of thyrotoxicosis that are mediated by sympathetic pathways. The sympatholytic agents phentolamine and dibenzyline have been reported both to depress and to stimulate thyroid function in animals. Their action is not clear, and it is of minimal clinical significance.[298-300] Among several α-adrenergic blocking agents tested, only phentolamine showed an inhibitory effect on the TSH response to TRH.[271]

Theoretically, thyroid hormone effects could be blocked by drugs which interfere with the tissue uptake of thyroid hormone or binding to its receptors. Inhibition of both cellular uptake and nuclear receptor binding has been demonstrated in vitro for amiodarone in hepatocytes and cultured pituitary cells. Inhibition of cellular thyroid hormone uptake has also been reported for calcium channel blockers and benzodiazapines. Furosemide and non-steroidal anti-inflammatory drugs reduce T3 binfding to cytosolic receptors. There is, however, no clear evidence that any of these drugs have a clinically significant effect on thyoid hormone action.

Among the multiple effects the ß-adrenergic blocker, propranolol, has on thyroid hormone economy, it appears to reduce the peripheral tissue responses to thyroid hormone (see also Chapters 3 and 11). Dinitrophenol enhances oxygen consumption by a direct effect on tissues and thus mimics one of the actions of thyroid hormone.[301]

Recent interest has been directed toward compounds which may share some but not all thyroid hormone actions by either selective tissue uptake or receptor binding. The general goal is to develop agents which promote weight loss or decrease lipids without adverse effects on the skeleton, heart (tachycardia) or pituitary (TSH suppression). [300a-300d] Diiodothyropropanoic acid (DIPTA) in short term studies was found to decrease cholesterol and lead to weight loss. [300a] However it was also found to increase bone turnover and reduce TSH, T3 and T4. [300a]

The drug eprotirome was shown to reduce total and LDL cholesterol, triglyerides and Lp(a) lipoprotein. [300b,300c] Eprotirome was not found to have adverse effects on the heart or bone and did not changed levels of TSH or T3 although mild, reversible dops in T4 levels were noted. [300b,300c] In a controlled trial, that was terminated prior to completion when adverse cartilage effects were noted in dogs, several patients did devlop transaminase elevations. [300c]

Specific Agents

Estrogens and selective estrogen receptor modulators (SERMs). Hyperestrogenism, either endogenous (caused by pregnancy, hydatidiform moles, or estrogen-producing tumors) or exogenous (due to the administration of estrogens), is accompanied by an increase in TBG and a decrease in TTR concentrations in serum.[220-222] Estrogens are the most common cause of TBG elevation, and this effect can be produced even after their topical application. The magnitude of TBG increase is in part dose related and occurs in women as well as in men. While tamoxifen blocks the estrogen induced increase of TBG[224a], tamoxifen alone in post-menopausal women increases TBG and T4 and 3 levels.[301a] . The selective estrogen receptor modulator (SERM) raloxifene, increases TBG, produces small increase in T4 and insignificant changes in free T4. [301b,301c] In a single case report, raloxifene appeared to also alter thyroid hormone absorption. [301d] Estrogen increases the complexity of oligosaccharide side chains and, as a consequence, the number of sialic acids in the TBG molecule which in turn prolongs its survival in serum.[302] The concentrations of other serum proteins, including several that bind hormones, such as cortisol-binding globulin and sex-hormone binding globulin, are also increased.[303]

The consequences of increased TBG concentration in serum are higher serum levels of T4, T3 and rT3 and, to a lesser extent, other metabolites of T4 deiodination. The fractional turnover rate of T4 is depressed principally due to an increase in the intravascular T4 pool. On the other hand, the FT4 and FT3 concentrations and the absolute amount of hormone degraded each day remain normal.[232,233] Transient changes in these parameters during the early changes in TBG concentration can be anticipated as described above. Some of the effects of pregnancy on thyroid function are also mediated by an estrogen-induced increase in the serum TBG concentration. The effects on thyroidal and renal

iodide clearance and BMR are mediated by different mechanisms (see Chapter 3).

The effect of estrogen, if any, on the control of TSH secretion is controversial. Contradictory results suggesting a stimulatory[304] and an inhibitory[305,306] effect have been obtained by different investigators and both stimulation and inhibition has been shown in a single study depending on the dosage utilized.[306a] In a study of the effects of Tamoxifen, TSH was elevated at 3 months but not at 6 months.[306b] Although women show a greater TSH responsiveness to TRH than men,[306-308] administration of pharmacologic doses of estrogens does not appear to have a significantly enhancing effect.[309,310] During ovarian hyperstimulation for ovulation induction, an increase in TSH and fT4 has been observed and this has been attributed to the marked increase in estrogen. [310a]

The effects of estrogens in the rat are not identical to those observed in humans. Estrogens do not induce changes in the concentration of serum T4-binding proteins in the rat.[22] Thus, investigations carried out in this species are not always representative in interpreting the effects of estrogens observed in humans

Androgens. Androgens decrease the concentration of TBG in serum and thereby reduce the level of T4 and T3.[223,311] The TTR concentration, however, is increased.[223] As with estrogens, the concentration of free hormone remains unaffected, and the degradation rate of T4 is normal at the expense of an accelerated turnover rate.[223] TSH levels are normal.[305] Anabolic steroids with weaker androgenic action have the same effect, although similar changes observed during danazol therapy have been attributed to its androgen-like properties.[224]

Salicylates. Acetylsalycilic acid has been identified as the most commonly administered medication which may cause significant alterations in measured parameters of thyroid function.[224b,224c] Salicylate and its noncalorigenic congeners (Fig. 5-3) compete for thyroid hormone-binding sites on serum TTR and TBG.[225-228] As a result, the serum concentrations of T4 and T3 decline and their free fractions increase.[228] The turnover rate of T4 is accelerated, but degradation rates remain normal.[225,226] Salicylate and its noncalorigenic congeners also suppress the thyroidal RAIU but do not retard iodine release from the thyroid gland.[312] The impaired respone to TRH[313] and the hypermetabolic effect[314] of salicylates have been attributed to the increase in the FT4 and FT3 fractions. If this were correct, hormonal release from the serum-binding proteins should produce only a temporary suppression of the thyroidal RAIU and transient hypermetabolism, but both effects are observed during chronic administration of salicylates.[225,226] In addition, this mechanism of action does not explain the lack of calorigenic effect of some salicylate congeners despite their ability to also displace thyroid hormone from its serum-binding proteins.

In vitro studies have demonstrated an inhibitory effect of salicylate on the outer ring monodeiodination of both T4 and rT3,[315] but lack of typical changes in serum iodothyronine levels suggests that this action is less important in vivo.

Acetylsalicylic acid mimics some actions of thyroid hormone, but does not reverse classic manifestations of hypothyroidism. While salicylate administration may lower serum cholesterol levels,[316] it does not provide a therapeutic effect in myxedema, or lower TSH levels.[317] Administration of 8 g aspirin daily raises the BMR to normal in myxedema, accelerates the circulation, and increases sweating, but it has no effect on the skin change, the electrocardiogram, or the mental state.[316]

Because of some analogies between the effects of salicylates and nitrophenol, uncoupling of oxidative phosphorylation has been suggested as one of its possible mechanisms of action. If this were the case, direct chemical action does not appear to be involved since analogs of salicylate that do not uncouple oxidative phosphorylation in vitro are active in vivo.[318]

p-Aminosalicylic acid and *p*-aminobenzoic acid are closely related chemically to salicylate. They inhibit iodide binding in the thyroid gland and are goitrogenic.[319,320] These agents also displace thyroid hormone from its serum protein-binding sites.[321] Abnormalities of thyroid function tests have been also

reported in patients treated with salsalate.[322]

Heparin. Patients receiving heparin chronically may have increased FT4 and FT3.[230,231] Reciprocal changes in serum TSH have been reported.[231] While it had been suggested that heparin might interact with the T4-binding proteins to alter the steric configuration of the binding sites and reduce the affinity of the proteins for T4 and T3[210], it is now thought that heparin acts via the activation of lipoprotein lipase to increase free fatty acid levels which may displace T4 from binding proteins. This effect is most likely to be significant when the levels of albumin are low and triglycerides are high such as during hyperalimentation with lipid solutions. Even low doses of heparin may be sufficient to cause artifactual, in vitro, increase in T4 especially when measured by equilibrium dialysis.[231a] Although initially reported with crude heparin preparations, this heparin effect has also been noted with enoxaparin. [231b]

Glucocorticoids. Physiologic amounts, as well as pharmacologic doses of glucocorticoids influence thyroid function. Their effects are variable and multiple, depending on the dose and on the endocrine status of the individual. The type of glucocorticoid and the route of administration may also influence the magnitude of the effect.[323] Known effects include (1) decrease in the serum concentration of TBG and increase in that of TTR;[324,325] (2) inhibition of the outer ring deiodination of T4 and probably rT3;[239,240] (3) suppression of TSH secretion;[246,326,327] (4) a possible disease in hepatic binding of T4; and (5) increase in renal clearance of iodide.[328,329]

The decrease in the serum concentration of TBG caused by the administration of pharmacologic doses of glucocorticoids results in a decrease in the serum total T4 concentration and an increase in its free fraction and the resin uptake test result. The absolute concentration of FT4 and FT4I remain normal. The more profound decrease in the concentration of serum T3 compared to T4 associated with the administration of pharmacologic doses of glucocorticoids cannot be solely ascribed to their effect on serum TBG. It is due to the decreased conversion of T4 to T3 in peripheral tissues. Thus, glucocorticoids reduce the serum T3/T4 ratio and increase that of rT3/T4 in hypothyroid patients receiving replacement doses of thyroid hormone.[239] This steroid effect is rapid and may be seen within 24 hours.[239,240] In rats, dexamethasone has been shown to decrease T4 to T3 conversion in liver homogenates. [329a]

Earlier observations of cortisone-induced depression of uptake and clearance of iodide by the thyroid[328,329] now are understood to be the result of steroid suppression of TSH secretion. Pharmacologic doses of glucocorticoids suppress the basal TSH level in euthyroid subjects and in patients with primary hypothyroidism, and decrease their TSH response to TRH.[246,326,327,329b] The latter effect is less marked in the presence of hypothyroidism.[327] Administration of as little as 34 mg. of hydrocortisone over 24 hours can be shown to reduce the pulse amplitude and mean TSH release the nocturnal rise of TSH and the T3 and TSH response to TRH.[329b] Administration of the glucocorticoid antagonist, mifepristone, produces an increase in TSH that remains within the normal range accompanied by a transient decrease in total but not free T4.[329c] Normal adrenocortical secretion appears to have a suppressive influence on pituitary TSH secretion because patients with primary adrenal insufficiency have a significant elevation of TSH.[330] In cultures from rat pituitary tumors, hydrocortisone increased the number of TRH receptors [331] Dexamethasone has also been shown to increase the transcription, translation and processing of TRH precursors. [331a,b] The mechanism of glucocorticoid action on the hypothalamic-pituitary axis is covered in Chapter 4.

No single change in thyroid function can be ascribed to a specific mode of action of glucocorticoids. For example, a diminished thyroidal RAIU may be due to the combined effects of TSH suppression and increased renal clearance of iodide. Similarly, a low serum TT4 level is the result of suppressed thyroidal secretion due to diminished TSH stimulation as well as the decreased serum level of TBG. One of the common problems in clinical practice is to separate the effect of glucocorticoid action on pituitary function from that of other agents and those caused by acute and chronic illness. This situation arises often since steroids are commonly used in a variety of autoimmune and allergic

disorders as well as in the treatment of septic shock. The diagnosis of coexisting true hypothyroidism is difficult, if not impossible. Due to the suppressive effects of glucocorticoids on the hypothalamic-pituitary axis, the low levels of serum T4 and T3 may not be accompanied by an increase in the serum TSH concentration, which would otherwise be diagnostic of primary hypothyroidism. In such circumstances, a depressed rather than an elevated serum rT3 level may be helpful in the detection of coexistent primary thyroid failure.

Pharmacologic doses of glucocorticoids induce a prompt decline in serum T4 and T3 concentrations in thyrotoxic patients with Graves' disease.[239] Amelioration of the symptoms and signs in such patients may also be accompanied by a decrease in the elevated thyroidal RAIU and a diminution of the TSH receptor antibody titer.[325,332] This effect of glucocorticoids may be due in part to its immunosuppressive action since it has been shown that administration of dexamethasone to hypothyroid patients with Hashimoto's thyroiditis causes an increase in the serum concentration of both T4 and T3.[333]

Iodinated contrast It is estimated that in the US in the past year more than 80 million CT scans were performed and more than half of those utilized iodinated contrast. Whether low or high ionic strength, low or high osmolality, all of these agents contain large amount of iodine ranging from 320 – 370 mg/ml. In a prospective study, 2.6% of adults receiving contrast developed hyperthyroidism although many of theses cases were transient. [333a] In a study of hospitalized elderly patients with hyperthyroidism, 23% of them had a contrast CT performed in the preceeding months. [333b] When Alexander et al examined a data base of 4,500,000 patients, they found that the likelihood of developing hyperthyroidism within two years of being euthyroid was doubled by having a recent contrast CT. [333c] In a small study, pretreatment with thionamides reduced the incidence and severity of hyperthyroidism but did not always prevent it. [333d] Since many episodes of hyperthyroidism after iodinated contrast are transient, mild and asymptomatic, this approach may only be appropriate for patients who had more severe episodes. Other options include avoidance of iodinated contrast and definitive treatment of any underlying thyroid disorder after the patient has recovered. In a study of newly diagnosed hypothyroidism in children, the risk was increased nearly three fold by recent administration of iodinated contrast, [333e] while in adults, Kornelius et al found the risk was doubled. [333f]

Ipodate and Iopanoic acid The principal effect of **these** iodine-containing radiologic contrast media is inhibition of T4 to T3 conversion by inhibiting both Type I and Type II 5'-deiodinase. In fact, they may be the most potent of all agents known to interfere with this step of iodothyronine metabolism. A triiodo-and a monoamino-benzene ring with a proprionic acid chain appear to be required because iodinated contrast agents without this chemical structure have little or no effect.[334] Several of these agents, namely, ipodate (Oragrafin) and iopanoic acid (Telepaque), are used for oral cholecystography.

A decrease in the rate of deiodination of the outer ring of thyronines causes a profound decrease in the serum T3 concentration and an increase in the rT3 and T4 levels.[334,335] The serum T4 concentration may reach values well within the thyrotoxic range.[334] These changes are accompanied by an increase in serum TSH secretion.[290] The latter is particularly notable, if not characteristic of these agents, probably because of their potent inhibitory effect on T3 generation in pituitary tissue.[58] These agents have been used to study the regulation of thyroid hormone action via the process of iodothyronine deiodination.[58,336] Changes persist for at least two to four weeks after their administration.[334]

Ipodate and iopanoic acid also decrease the hepatic uptake of T4[337] and inhibit T3 binding to its nuclear receptors.[338] These effects reduce both symptoms and thyroid hormone levels even when thyrotoxicosis occurs in settings where ongoing synthesis would be minimal such as thyrotoxicosis secondary to thyroid hormone ingestion[338a] , or sub-clinical hypothyroidism. [338b] The antithyroidal effect of the iodine present in these agents is believed to be responsible for the falling T4 level and some of

the amelioration of the symptoms and signs of thyrotoxicosis when they are administered to patients with Graves' disease[338,338c,338d],

Amiodarone. Most changes in thyroid function observed during the administration of this drug are similar to those seen with iodine-containing contrast agents. They include a marked decrease in serum T3, an increase in rT3, and a more modest elevation in the T4 concentration.[241,339] Basal and TRH-stimulated TSH levels are increased. The principal mechanism of action is believed to be inhibition of both Type I and Type II 5'-deiodinase resulting in a marked reduction of T3 generation from T4. Amiodarone may reduce the entry of thyroid hormone into tissues[339a], may reduce the binding of thyroid hormones to the receptor[339b] and may antagonize the effects of thyroid hormone at the cellular level.[339c,339d] The drug is used as an antianginal and antiarrhythmic agent and the bradycardia that almost invariably occurs when the drug is used in high doses, may suggest the presence of hypothyroidism.[340]

Amiodarone contains 37% iodine by weight. The major effects on thyroid function appear to be the result of its structural resemblance to thyroid hormone rather than its iodine content. In contrast to the typical alterations of thyroid hormone function, the more uncommon occurrence of frank hypothyroidism or thyrotoxicosis are products of the excess iodine released from the drug. The overall incidence of amiodarone induced thyroid disease is higher in areas of mild iodine deficiency[340] as is the relative incidence of the thyrotoxic as compared to the hypothyroid form. [340] The iodine dependence of both of these diseases is confirmed by the improvement of both with the use of perchlorate to discharge iodine from the thyroid gland. [340a, 340b]

Amoidarone induced thyrotoxicosis has been identified as having two main types; type 1 usually coccuring with underlying thyroid abnormalities and type 2 in normal glands with small goiters. [340a, 340b] Type 1 is more common in area of iodine deficiency. Early onset of thyrotoxicosisis is more typical for Type 1 and later onset with Type 2, but either form may present after amiodarone was discontinued. [340c, 340d] Type 1 is associated with increased blood flow while hypervasculaity is absent in Type 2. Radioacitve iodine uptake may be low-normal or normal in Type 1 (especially in areas with iodine deficiency) and is low in Type 2. Type 1 is treated with thionamides but patients may be realtively resistant while patients with Type 2 respond to glucocorticoids. Some patient will present with a mixed form. Surgery may be used in cases refractory to medical therapy. [340e]

Measurement of serum TSH, remains the most useful test in the differential diagnosis of hypothyroidism or thyrotoxicosis in amiodarone treated patients but the mild TSH elevation seen in euthyroid patients may make the diagnosis of mild to moderate hypothyroidism more difficult. If hypothyroidism is suspected, it is appropriate to obtain a measurement of the serum rT3 concentration. The absence of an elevated serum rT3 level in a patient receiving amiodarone suggests the patient is hypothyroid.

Diphenylhydantoin (Dilantin). Diphenylhydantoin (DPH) (Fig. 5-3) competes with thyroid hormone binding to TBG.[228,229] This effect of DPH and diazepam, a related compound, has been exploited to study the conformational requirements for the interaction of thyroid hormone with its serum carrier protein[229,341] It appears that the angle formed between the two phenyls and the hydantoin group of DPH is nearly identical to that formed between the two phenyls linked by an ether bond in T4.[229] Although the affinity of DPH for TBG is far below that of T4, when used in therapeutic doses the serum concentration achieved is high enough to cause a significant occupancy of the hormone-binding sites

on TBG. This effect of DPH is only partly responsible for the decrease in the total concentration of T4 and T3 in serum.

DPH accelerates the conjugation and clearance of T4 and T3 by the liver and probably enhances the conversion of T4 to T3.[247,342] The net result is a decrease in the serum concentration of T4 and rT3 and, less consistently, that of T3[343,344,344a,344b] because the enhanced degradation of T3 is compensated for by an increase in its generation from T4. Yet, basal TSH- and TRH-stimulated values remain within the normal range[343,344,344a,344b] or slightly elevated.[235,345] Calculated indices of FT4 are usually reduced, but the FT4 measured by dialysis is normal.[247,343]

Both DPH and diazepam are commonly used in clinical practice, the former most commonly as an anticonvulsant and the latter as an anxiolytic. Reduced serum levels of thyroid hormone in patients having therapeutic blood levels of DPH should not be viewed as indicative of thyroid dysfunction unless the TSH level is elevated. Treatment with T4 in such patients with a low T4 and normal TSH did not alter parameters of cardiac function or symptoms which might have been considered indicative of hypothyroidism.[344b] DPH therapy may increase the required dose of thyroid hormone replacement in athyreotic individuals.[346] .

Phenobarbital. Chronic administration of phenobarbital to animals induces increased binding of thyroid hormone to liver microsomes and increased deiodinating activity.[248,249,347,347a] Phenobarbital administration reduces the biologic effectiveness of the hormone by diverting it to microsomal degradative pathways. In humans, phenobarbital augments fecal T4 clearance by nearly 100%,[348] but serum T4 and FT4 levels remain near no rmal because of compensatory increases in T4 secretion. It is not apparent that barbiturates have an important effect on thyroid mediated metabolic action in normal humans, but it may potentate the effects of dilantin or carbamazapine. [348a] The augmented hepatic removal of T4 induced by phenobarbital lower the absolute T3 disposal by nearly 25%, increase T4 clearance, and lower T4 and FT4I in patients with Graves' disease but does not produce a clinical response.[348]

Propranolol. Propranolol, a ß-adrenergic blocker, is commonly used as an adjunct in the treatment of thyrotoxicosis Propranolol is usually used in the treatment of cardiac arrhythmias, angina and hypertension. Information regarding its effects on thyroid hormone action, and application in the symptomatic treatment of thyrotoxicosis is found in Chapters 3 and 11, respectively.

Propranolol does not affect the secretion or overall turnover rate of T4, nor TSH release or its regulatory mechanisms.[349,350] A small to moderate lowering effect on serum T3 has been reported in euthyroid subjects as well as in patients with hyperthyroidism or with myxedema under L-T4 replacement therapy.[243,245,351,352] Reciprocal increases in serum rT3 and 3',5'-T2 levels have also been reported.[352] Such data, combined with the finding by some investigators of minimal increases in serum T4[245] levels, suggest a mild blocking effect of this drug on the 5'-deiodination of iodothyronines. This effect does not appear to be related to the ß-adrenergic-blocking action of propranolol, since other ß-blocking agents do not share the deiodinase-blocking property and yet are effective in treating symptomatic thyrotoxicosis.[353,354] The beneficial effects include the reduction of tachycardia, anxiety, and tremor [355-357] although the metabolic effects of thyrotoxicosis remain unaffected.

Reserpine. Reserpine formerly had wide use as an antihypertensive agent but has been replaced by more effective agents. Reserpine alters the manifestations of thyrotoxicosis by reducing anxiety, tachycardia, and tremulousness.[358] This effect may arise from depression of autonomic centers or possibly from depletion of catecholamines in the peripheral tissues.[359] Reserpine may depress the formation of iodotyrosines in thyroid tissue in vitro, but this action does not seem to be important clinically. Reserpine does not alter the results of thyroid function tests other than the BMR.[358]

Nitrophenols. 2,4-Dinitrophenol (Fig. 5-3) elevates the BMR, lowers the serum concentration of T4,

accelerates the peripheral metabolism of T4, and depresses the thyroidal RAIU and secretion.[275,360,361] The action is probably complex. The drug stimulates the metabolism by uncoupling oxidative phosphorylation in mitochondria.[362] T4 in vitro also uncouples oxidative phosphorylation. Part of the effect of dinitrophenol may be to mimic the action of thyroid hormone on hypothalamic or pituitary receptor control centers; this effect would account for the diminished thyroid activity. Dinitrophenol also displaces thyroid hormone from T4-binding serum proteins.[227] This action could lower the total hormone concentration in serum but should have no persistent effect on thyroid function. Dinitrophenol increases biliary and fecal excretion of T4, and this action largely accounts for the rapid removal of hormone from the circulation.[363] Deiodination of T4 is also increased.[364] Both of these effects may be related to displacement of hormone from TTR or to changes in metabolism of hormone in the liver.

2,4-Dinitrophenol does not share some of the most important properties of T4. It cannot initiate metamorphosis of tadpoles[365] or provide a substitute for hormonal therapy in myxedema.

Dopaminergic Agents. It is generally accepted that endogenous brain dopamine plays a physiologic role in regulating TSH secretion via an effect on the hypothalamic-hypophyseal axis.[252,366,367] Dopamine exerts a suppressive effect on TSH secretion and can be regarded as antagonistic to the stimulatory action of TRH at the pituitary level.[284,287,367] Much of the information regarding the role of dopamine on the control of TSH secretion in humans has been derived from observations made during the administration of agents with dopamine-agonistic and -antagonistic activity (see Table 5-4 and Chapter 4).

Dopamine infusion is commonly used in the care of acutely ill hypotensive patients. It lowers the basal serum TSH level in both euthyroid and hypothyroid patients and blunts its response to the administration of TRH.[252,284,287,368,368a]

L-dopa, the precursor of dopamine, used in the treatment of Parkinson's disease and as a test agent in the diagnosis of pituitary diseases, also suppresses the basal and the TRH-stimulated serum TSH level in euthyroid subjects as well as in patients with primary hypothyroidism[285,288,368b] (Fig. 5-5). Metoclopropamide, a dopamine antagonist used as a diagnostic agent and in the treatment of motility disorders, increased TSH secretion. [368c]

A similar effect has been observed during the administration of 2-brom-ergocryptine (bromocryptine), a dopamine agonist used in the treatment of some pituitary tumors and to suppress lactation during the puerperal period. Although the agent has been shown definitely to diminish the high serum TSH levels in patients with primary hypothyroidism,[286] a significant inhibitory effect on TRH-induced TSH secretion has not been clearly demonstrated,[369,370]

The exact mechanism whereby dopaminergic drugs inhibit pituitary TSH secretion remains unknown, although a direct interaction with pituitary receptors has been suggested.[371] While some authors have cautioned that prolonged infusion of dopamine may induce secondary hypothyroidism and worsen the prognosis of severely ill patients,[372] there is no evidence that chronic treatment with dopaminergic drugs induces hypothyroidism in less critically ill patients.[288] These drugs have been used with variable success in the treatment of some rare pituitary-induced thyrotoxicoses.[373,374] When measurements of the basal or stimulated serum TSH levels are used in the differential diagnosis of primary and secondary hypothyroidism, the concomitant use of drugs with dopamine-agonistic or -antagonistic activity should be taken into account in the interpretation of results.

Alterations of Immunity

A number of drugs including interferon and lithium affected thyroid function either in part or completely by inducing thyroid immunity. In the past few years a number of agents have been developed to treat cancer and multiple sclerosis by altering immune regulation. Unintended side effects or these drugs has been the development of hyperthyroidism from Graves' disease or thyroiditis and hypothyroidism as a consequence of autoimmune hypophyisitis or chronic thyroiditis.

Interferon and Interleukin These cytokines have been associated with the development of both hypothyroidism and thyrotoxicosis. [375-379] The overall rate of thyroid dysfunction induced by these agents is about 6%.[379a] They are used in the treatment of infectious diseases such as hepatitis, as well as malignancies including melanoma and renal cell carcinoma . Acute administration has been used as a model of illness as the effects are similar; interferon-α leads to a decrease in T3 an increase in rT3 and a fall In TSH. [380] In a group of euthyroid HIV infected patients, however, short term administration of interleukin-2 was observed to lead to an increase in TSH, T3, T4 and free T4. [381]

Cytokine induced thyroid disease appears to be immune mediated. The incidence is much greater in females and in patients with positive anti-peroxidase and anti-TPO antibodies prior to the initiation of therapy. [375-377] During therapy, patients who were antibody positive may have a rise in titer, while antibody positivity may develop in previously negative patients.[375] In patients treated **for hepatitis** with interferon, the incidence of thyroid disease is much higher in those with Hepatitis C than those with Hepatitis B.[375] The thyrotoxicosis often occurs as a manifestation of a destructive thyroiditis.[376-377] In many patients, the thyroid disease resolves within several months after stopping the cytokine therapy. [375,377]

Anti CD 52 Antibody Alemtuzumab This monoclonal antibody reacts against CD52, a glycoprotein that is expressed on B cells and CD4+ T cells. It is approved by the FDA for the treatment of multiple sclerosis. It is initially dosed daily for five days and then a second course is given for three days, one year later.

Thyroid disease has been noted to occur in a third of treated patients with some cases seen within weeks of initiating treatment and most cases seen within the first three years but cases have been seen up to seven years after starting treatment. [376a,376b,377a]

The most frequently observed disorder has been Graves' disease which affects almost a quarter of all treated patients. [376a,376b,377a] Most affect patients develop antibodies. Most cases are overt and some patients have experienced significant ophthalmopathy. While as many as 35% of these patients have been reported to have spontaneous resolution, most have been treated medically. Hypothyroidism develops in 5-7% of patients. Most of these patients develop anti-thyroid antibodies and the deficits are usually permanent. Less than 5 % of patients will develop typical painless thyroiditis with transient hyperthyroidism sometimes followed by hypothyroidism. [376a,376b,377a]

Check Point Inhibitors

These agents target systems that normally act to limit activation of the immune system but are utilized by cancer cells to block immune mediated destruction. Use of these agents allows the activated immune cells to kill tumor cells. . [377b- 377d] The same mechanism of action, however, leads to activation of immune mediated damage to other cells including skin, liver and thyroid cells. . [377b- 377d]

Antibody against CTLA-4 ipilimumab Co-stimulation via HLA and B7 expressed on antigen presenting cells (and tumor cells) interacting respectively with T cell receptors and CD 28 expressed on T-cells leads to T-cell activation. Activated T-cells then express CTLA-4 that competes with CD 28 for B7 binding and thus reduces T cell activation. The monoclonal antibody, ipilmumab, specifically binds to CTLA-4 markedly enhancing T cell activation. [377b- 377d] This promotes immune-mediated destruction of tumor cells. This agent was approved by the FDA for the treatment of melanoma in 2011. Usual

dosing is every three weeks for four doses. The drug also remains under investigation for treating other tumors.

The most common associated autoimmune disorder affecting the thyroid has been the development of hypophyisitis. [377b- 377f] Prior to the introduction of this agent, autoimmune hypophyisitis was typically seen in women in late pregnancy or post-partum, while hypophysitis secondary to ipilimumab has been seen almost solely in men. Onset has been within weeks of initiating therapy until almost two years later. [377b- 377f] Most patients present with systemic symptoms while some present with headaches or visual symptoms. MRI abnormalities are common and include pituitary enlargement and stalk thickening. Similar to post-partum hypophyisitis, the pituitary-adrenal axis is most commonly affected, but most deficits are permanent. [377b- 377f]

Hypothyroidism occurs in 4-6% of treated patients from 2 months to 3 years after starting treatment. Fatigue is the most common presenting symptom. The hypothyroidism is usually permanent. Some 1-3 % of treated patients will develop typical painless, thyroiditis with transient hyperthyroidism. Onset is usually two to four months after starting treatment. [377b- 377f] Hyperthyroidism is sometimes followed by hypothyroidism. The package insert advises checking thyroid function prior to starting therapy, before each dose and as "clinically indicated'" but does not recommend checking cortisol or ACTH.

Antibodies Against Programmed Death Receptor Ligand (PDL-1) Pembrolizumab and Nivolumab
Recognition of tumor cells via MHC/T cell receptor interaction leads to T cell activation and interferon production which stimulates tumor cell production of the PD-1 ligand. This then binds with the PD-1 receptor on the T cell and inhibits activation. Dendritic cells also express this ligand to inhibit T-cell activation. Pembrolizumab and Nivolumab are monoclonal antibodies directed against the PD1 ligand that act to increase T-cell activity and thus promote immune-mediated destruction of tumor cells. [377d, 377g] These drugs were approved by the FDA in 2014 for the treatment of melanoma. Pembrolizumab is administered intravenously every 3 weeks. Nivolumab is administered intravenously every 2 weeks. These drugs also remains under investigation for treating other tumors.

Both agents may lead to the development of immune mediated hypothyroidism, thyroiditis and hypophysitis with hypothyroidism being the most common problem. [377g-377i] Hypothyroidism may occur within weeks of starting therapy or may not occur until after a year. It is usually permanent. [377g-377i] In contrast, reported cases of hyperthyroidism from thyroiditis have occurred from 2 weeks to 5 months after initiating therapy and always resolves. [377g-377i]

For pembrolizumab the occurrence of these complications has been reported as 8% for hypothyroidism, 2-3% for thyroiditis and 0.5% for hypophyisitis. For nivolumab the rate of occurrence of these complications have been reported as 4-8% for hypothyroidism and 1-3% for thyroiditis. For both drugs, it is recommended to check thyroid function tests prior to starting therapy and periodically afterwards.

Tyrosine Kinase Inhibitors Sunitinib maleate an oral tyrosine kinase inhibitor used in the treatment of renal cell carcinoma and gastrointestinal stromal tumors has also been associated with the development of hypothyroidism.[381a] In two studies, an elevated TSH has been seen in over 50% of patients treated with sunitinib. [382.383] In a prospective study, this was persistent in 36% and transient in 17%. [382] The mechanism remains unknown. [382a] Antiperoxidase activity was demonstrated in vitro[382], but other mechanisms include induction of destructive thyroiditis, [383] reduction of vascularity ot the gland, [383b] and enhanced apoptosis. [383c]

The thyroid effects are seen with other TK inhibitors as well although the frequency and severity of the

effect may vary. Hypothyroidism has also been seen with Sorafenib, but the rate is about 1/3 of that seen with sunitinib.[383d,383e] In a few patients, transient thryotoxicosis has preceeded the hypothyroidism consistent with a destructive thyroiditis. [383d] There is also evidence for enhanced thyroid hormone metabolism attributed to increased Type 3 deiodination. [383f] This would also explain the need for increased thyroid hormone doses in athyreotic thyroid cancer patients.

Imatinib mesylate is a selective tryrosine kinase inhibitor used in the treatment of chronic mylogenous leukemia (CML) and other malignancies. Thyroidectomized patients being treated with imatinib were noted to have a rise in TSH and a fall in serum T4 levels which responded to an increase in the T4 dose, suggesting enhanced metabolism of thyroid hormone [384] but changes have also been seen in euthyroid patients. [384a] In most, cases, these changes were transient (74%) but have persisted in others. [384a] Even higher rates of thyroid dysfunction have been seen with the newer agents nilotinib (55%) and dasatinib (75%). [384a] As with the other TK inhibitors some patients have had thyrotoxicosis and some have developed antithyroid antibodies. [384a]

Retinoids Bexarotene is a retinoid which is specific for the retinoid X- receptor and is used for the treatment of lymphomas and other malignancies. Therapy has been reported to produce central hypothyroidism [376a,376b,385], and a single dose, leads to a decrease in T3, T4 and TSH. [386] In addition to suppression of TSH synthesis and secretion, bexarotene also increases the peripheral metabolism of thyroid hormone by a nondeiodinase mediated pathway. [387]

TSH Receptor Agonists and Antagonists A number of small molecules that interact with the TSH receptor were identified and characterized to select compounds which could behave as TSH receptor agonists or antagonists. [387] These were then further modified to increase their activity. Of note, these molecules do not bind to the TSH ligand binding region but rather to the serpentine trans-membrane region of the receptor. These compounds have multiple potential uses including use as imaging agents for thyroid cancer and Graves' ophthalmopathy and as therapeutic agents for patients with Graves' or thyroid cancer.

A TSH receptor agonist has been developed that when added to primary cultures of human thyrocytes increased messenger RNA expression for thyroglobulin, the sodium-iodide symporter, thyroid peroxidase (TPO), and deiodinase 2 similar to TSH. [388] When administered orally to mice, this compound increased radioactive iodine uptake in the thyroid and serum T4. [388] As an oral agent, this compound could potentially be used for imaging and treatment of thyroid cancer rather than parenteral rTSH or thyroid hormone withdrawal.

A TSH receptor antagonist has also been developed that has activity both in cells overexpressing the human TSH receptor and in primary cultures of human thyrocytes. [389] The compound reduces both basal and TSH stimulated cAMP production. Recently it was demonstrated in cultured human thyrocytes to reduce basal TPO mRNA expression and to antagonize the effect of sera from Graves' patients to induce TPO mRNA expression. [389] As an oral agent, this compound could potentially be used for imaging, to treat Graves' patients or to suppress thyroid cancer without requiring use of supraphysiologic T4 doses.

Thyronamines Thyronamines are small molecules identical to thyroxine, triiodothyronine and all of the deiodinated thyroid hormone metabolites except that they lack a carboxyl moiety at the amino terminus (ethylamine rather than alanine group). [390] Each compound is identified similar to the corresponding thyroid hormone or metabolite as T_X(AM) where X is the number of iodine molecules and ranges from zero, T_0(AM), to four, T_4(AM). Two of these compounds, [3-T_1(AM) and T_0(AM)], have been identified

by liquid chromatography-tandem mass spectrometry as naturally present in small amounts in tissues and sera from hamsters, mice and rats. [390] They have been detected in both cardiac and brain tissue. [390] No published report has confirmed the presence of any of these compounds in humans. It has been speculated that some of these compounds could be directly produced by the decarboxylation of T4 or T3, but this has never been demonstrated. These compounds can be deiodinated, in vitro, by Deiodinases 1, 2 and 3. [390]

These compounds can bind to a number of receptors and 3-T_1(AM) binds strongly to APO B 100 in serum. Despite the structural similarities to thyroid hormones, the thyronamines do not bind to nuclear thyroid hormone receptors and they do not alter T3 binding to these receptors. [390] Several thyronamines bind to the beta-adrenergic receptor, but any effects on cAMP signaling remain unclear. [390] There is conflicting evidence regarding the ability of these compounds to signal via the trace amine associated receptor 1 (TAAR-1) or via the $Alpha_{2A}$ adrenergic receptor. [390] There is also conflicting evidence about the ability of these compounds to alter intracellular signaling via the cAMP or tyrosine phosphorylation or dephosphorylation pathways. [390]

There are no known physiologic actions of any of these compounds. In animals, several of these compounds have been found to have pharmacologic activity both in vitro and after intraperitoneal or intraventicular injection. These observations include a reduction in cardiac contractility and rate, a reduction in the metabolic rate, a reduction in fat mass and the development of hypothermia, ketonuria and hyperglycemia. [390] Many of these activities are noted within minutes after injection and resolve after a few hours but the development of ketonuria and the reduction of fat mass occur later and persist longer. [390] Potential therapeutic uses of these compounds are being evaluated in animal models. The ability of these compounds to induce hypothermia, has been shown to decrease infarct size when they were administered 2 days before or 1 hour after the induction of a stroke in an animal model. [390]

Metformin Metformin is a biguanide used in the treatment of diabetes mellitus as well as insulin resistance and polycystic ovary syndrome. In four patients with hypothyroidism on stable thyroxine therapy, TSH levels became markedly reduced with either no change in serum thyroid hormone levels or despite a reduction in the T4 dose and serum thyroid hormone levels suggesting a direct suppression of TSH release. [388] Subsequent studies have reported mixed effects, but a meta-analysis conluded that TSH alterations are seen in both overt and sub-clinical hypothryoidism but not in euthyroid patients suggesting an effect to suppress TSH that is not seen when the thyroid gland is able to respond to any change in TSH. [388b]

Biotin Biotin is a B vitamin that acts as a cofactor for carboxylase enzymes involved in gluconeogenesis and fatty acid synthesis. It is produced by gut bacrteria and normal daily intake is 35-350 mcg daily. It is used in the treatment of biotinidase deficiency and proprionic acidemia and as a supplement for TPN. It is frequently used by individuals in doses of 5,000 to 10,000 mcg daily as a supplement to improve hair and nail growth and to treat hair and nail disorders

Many laboratory platforms for the measurement of fT4, fT3 TSH and thyroglobulin depend on the strong binding of biotin and strep avidin. If patients ingest biotin in doses of 5,000 to 10,000 mcg prior to blood being drawn for these analytes, measurements of fT4 and fT3 will be falsely high and thyroglobulin and TSH will be falsely low as biotin interferes in the assays. . [397,398] The combination of a high fT4 and low TSH mimics hyperthyroidism. [397-400] These effects correspond to the blood level of biotin with a peak effect seen several hours after ingestion and potentially even lasting until the next day. [398,400] Variable times between ingestion and blood measurements can results in confusing variations in these measurement not corresponding to patents clinical status. Confirmation of this effect can be made by measuring several hours after ingestion and after abstaining for 48 hours or by re-measuring

in an assay not utilizing biotin. [397-400] This effect is not limited to thyroid hormone measurements but have also been reported for PTH, DHEA-sulfate, estradiol and ferritin. [398]

SUMMARY

This chapter considers the effects of various environmental factors, drugs and chemicals, and nonthyroidal diseases on thyroid function.

In animals, cold exposure causes a prompt increase in TSH secretion, which gives rise to thyroid hormone release and leads to thyroid gland hyperplasia. Part of this effect is due to an apparent increase in the need for thyroid hormone by peripheral tissues and to an excessive rate of hormone degradation and excretion. In humans, hypothermia causes a dramatic TSH secretion in the newborn, but this response is lost after the first few years of life. Exposure to heat has an opposite effect, although of lesser magnitude. A small seasonal variation in serum thyroid hormone levels that follow this general pattern has been reported.

Simulated altitude and anoxia depress thyroid hormone formation in rats, but in humans serum T4 and T3 concentrations, T4 degradation, and oxygen consumption are at least temporarily augmented by high altitude.

Starvation has a profound effect on thyroid function, causing a decrease in serum T3 concentration and a reciprocal increase in rT3 level. These changes are due to a selective inhibition of the 5'-monodeiodination of iodothyronines by peripheral tissues. Reduction in carbohydrate intake rather than total calorie deprivation appears to be the determinant factor. These alterations in thyroid function are believed to reduce the catabolic activity of the organism and thus to conserve energy in the face of decreased calorie intake. Chronic malnutrition is accompanied by similar changes. Overfeeding has opposite although transient effects.

Physical and emotional stresses can have variable and opposite effects. Increased thyroid hormone secretion and serum levels have been observed in stressed animals and in acute psychiatric patients on admission. The physical stress of surgery causes a prompt decrease in the serum T3 concentration, probably as a consequence of decreased T3 neogenesis. This effect of surgery cannot be fully explained on the basis of increased adrenocortical activity or calorie deprivation.

Many minerals alter the synthesis of thyroid hormone, mainly through their interference with iodide concentration and binding by the thyroid gland. The action of iodine is only briefly covered here since it is discussed in Chapters 2 and 13. Calcium, nitrate, bromine, rubidium, and fluorine are allegedly goitrogenic. Lithium carbonate, used in the usual doses for the treatment of affective disorders, can produce goiter in susceptible persons. It inhibits iodide binding and hormonal release from the thyroid gland, probably through a synergistic action with iodide.

Numerous dietary goitrogens, including cyanogenic glucosides, thioglucosides, thiocyanate, and goitrin, are present in a wide variety of foods, and are believed to contribute to the occurrence of endemic goiter in some areas of the world. Monovalent anions such as thiocyanate and perchlorate inhibit iodide transport into the thyroid and cause goiter.

Thionamide drugs such as PTU and the related compound, methimazole, inhibit thyroid peroxidase and thus prevent thyroid hormone synthesis. In addition, PTU but not methimazole inhibits the conversion of T4 to T3 in peripheral tissues. Under appropriate circumstances, sulfonamides, sulfonylureas, salicylamides, resorsinol, amphenone, aminoglutethamide, antipyrine, aminotriazole, amphenidone, 2,3-dimercaptopropanolol, and phenylbutazone have antithyroid action.

A growing list of drugs and diagnostic agents have been found to affect thyroid economy by modulating the regulation of the hypothalamic-pituitary-thyroid axis, as well as by interfering with thyroid hormone transport, metabolism, excretion, and action. Some drugs, such as salicylates, diphenylhydantoin, and glucocorticoids, act at several levels. Several compounds, most notably estrogens, diphenylhydantoin, diazepam, heparin, halophenate, fenclofenac, and some biologically

inactive thyroid hormone analogs compete with binding of thyroid hormone to its carrier proteins in serum. The only consequence of drugs affecting hormone transport is a decrease or increase in the concentration of total but not free hormone in serum.

Glucocorticoids, drugs such as propranolol, and amiodarone and some iodinated contrast media inhibit the extrathyroidal generation of T3. The result is a decrease in serum T3 and an increase in rT3 concentrations, with a slight increase or no change in T4 values. Thyroid hormone disposal is accelerated by diphenylhydantoin and phenobarbital, which increase several of the pathways of hormone degradation, and by hypolipemic resins, which increase the fecal loss of hormone. Homeostasis is usually maintained by a compensatory increase in thyroid hormone secretion.

Some drugs act through inhibition or stimulation of TSH secretion. Most notable of the former effect are dopamine agonists such as L-dopa and bromocryptine, as well as some a-adrenergic blockers, glucocorticoids, acetylsalicylic acid, and opiates. A variety of dopamine antagonists as well as cimetidine, clomifene, and spirolactone appear to increase TSH secretion. These compounds seem to interfere with the normal dopaminergic suppression of the hypothalamic-pituitary axis. Observed changes in TSH secretion are not associated with significant metabolic alterations. Some of the drugs have an apparent effect on TSH secretion through changes induced at the levels of the free and active forms of the thyroid hormone. A handful of drugs appear to block or antagonize the action of thyroid hormone on tissues. These drugs include guanethidine, propranolol, and dinitrophenol. Some drugs may induce autoimmune thyroid disease. Notably among these are lithium, interferon, interleukin, alemtuzumab. prembrolizumab and nivolumab.

The clinician should be thoroughly familiar with the effects of drugs, nonthyroidal illnesses, and other extraneous factors on thyroid function. These factors should all be taken into account in the differential diagnosis of primary thyroid disease.

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