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The Effects of Drugs on the Distribution and Metabolism of Thyroid Hormones

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I. Transport and Distribution of Thyroid Hormones

Thyroid hormones in plasma and tissues exist almost entirely in bound form. The binding is noncovalent and rapidly reversible, so that the hormones are in a dynamic exchange between the vascular, interstitial, and cellular compartments. The partition of hormone between extracellular and intracellular compartments is determined by the relative strength of binding to the plasma proteins on one hand and to the cellular binding sites on the other hand. A host of pharmacological agents influence the distribution of thyroid hormones by inhibiting binding to specific plasma proteins, by altering the concentration of such proteins, by changing the number or affinity of cellular binding sites, or by a combination of these effects. Before discussing effects of particular drugs, we will consider in a general way the physiological consequences of alterations in hormone binding and distribution.

A. Plasma Binding Proteins

In human plasma the principal thyroid hormone-binding proteins, in decreasing order of affinity, are: thyroxine-binding globulins (TBG), thyroxine-binding prealbumin (TBPA), and albumin. Each of these proteins binds both L-thyroxine (3,5,3′,5′-tetraiodo-L-thyronine) (T_4) and 3,5,3′-triiodo-L-thyronine (T_3), but the affinity for T_4 is in each case about 10 times higher than that for T_3 (266a, 293). The binding capacity (i.e. number of total sites per unit volume of plasma) is inversely related to the binding affinity. Thus, TBG has the lowest capacity (by virtue of its low concentration in plasma) and albumin has the highest capacity (117a). The distribution of each hormone among these three proteins is determined by both the affinity and the concentration of each protein. Under conditions that obtain in vivo, TBG binds about 70% of the T_4 and 60% of the T_3 in plasma, TBPA binds about 15% of T_4 but less than 5% of the T_3 (78), and albumin binds almost all of the remainder of both hormones.

The proportion of total hormone that exists in the free, unbound form, estimated by equilibrium dialysis of plasma, is approximately 0.03% for T_4 and 0.3% for T_3 (266a). There is a large body of evidence (beyond the scope of this review) to support the idea that the circu-

lating concentration of free thyroid hormone, rather than that of the bound fraction, determines the amount available to cells. Specifically, the rate of transcapillary passage of thyroid hormone (289) and the rate of uptake (unidirectional clearance) by tissues (52a, 52b) correlate with the free rather than with the total or bound fraction of circulating hormone. During its transit through an organ (e.g. the liver) a portion of the hormone bound to relatively weak binding sites (TBPA, albumin) dissociates and becomes available for uptake by cells (152, 154, 252a). The rates of dissociation of T_4 from low-affinity binding sites and of T_3 from TBG and albumin have been shown to be sufficiently rapid to account for the observed rates of uptake of free hormone by tissues such as the liver (152, 154, 252a). Although it has been generally assumed that thyroid hormones enter cells by a process of passive diffusion, recent reports describing saturable, specific, and high-affinity binding of T_4 (118) and T_3 (258) by isolated plasma membranes or by intact liver cells (184a) raise the possibility that carrier-mediated transport may also play a role. Evidence for receptor-mediated endocytosis of T_3 in cultured mouse fibroblasts has also been presented (55a).

B. Tissue Binding

Nearly all of the T_4 and T_3 in tissues is associated with cellular components, including membranes, organelles, and soluble proteins. A small fraction of intracellular hormone exists in free form. There are important differences between T_4 and T_3 in respect to tissue distribution. In humans, about one-third of the total extrathyroidal pool of T_4 is intracellular. The liver accounts for more than 80% of the total cellular T_4; most of the remainder is distributed in kidney, skin, and muscle (236). In contrast, T_3 is largely intracellular; only about 15% is extracellular. Most of the cellular T_3 is in kidney, muscle, and skin; relatively little is in the liver (52b). The fact that T_4 is largely extracellular and T_3 intracellular is a consequence of both weaker plasma binding and stronger cellular binding of T_3 compared to T_4. It has been estimated that intrinsic binding of T_3 by the composite cellular compartment is about twice as strong as that of T_4, both in humans and in rats (242). The intracellular distribution of thyroid hormones has received much attention. Low-capacity, high-affinity T_3-binding sites have been identified in the nuclei (238), plasma membrane (258, 118), mitochondria (299), and cytosol (136). In contrast to plasma binding proteins, these sites have a higher affinity for T_3 than for T_4. In addition to these cellular components, the endoplasmic reticulum of liver is a high-capacity, low-affinity binding system and accounts for a considerable proportion of intrahepatic hormone, about 40% of T_4 and T_3 (237). This "microsomal" fraction of liver, as we shall discuss, is especially important in the metabolism of thyroid hormones.

C. Consequences of Altered Plasma and Tissue Binding

A primary increase in the plasma concentration of TBG leads to a change in the ratio of free to bound T_4 in favor of the bound form. Even a momentary decrease in free T_4 would lead to a decrease in cellular uptake of hormone and a shift out of rapidly exchangeable tissue compartments into the circulation. This shift together with a transient slowing in the metabolic disposal of T_4 (due to a decrease in cellular T_4 pools) lead to a gradual restoration of free T_4 toward the normal baseline level (assuming no fall in T_4 supply). Thus, a new steady state is established with a higher level of TBG-bound T_4, normal free T_4 concentration, and normal tissue T_4 pool size. With an intact pituitary-thyroid axis, the transient decline in free T_4 concentration that follows a primary increase in TBG would hasten the achievement of the new steady state. However, the intervention of the pituitary-thyroid mechanism is not necessary for the restoration of the free hormone level. The same sequence of events, i.e. a shift toward bound T_4 and temporary decline in T_4 disposal until circulating free T_4 is restored to normal, would follow an increase in TBG even in athyreotic individuals maintained on a constant replacement dose of T_4 (162a).

A primary *decrease* in net plasma binding of T_4, due either to a decline in the concentration of TBG or to the presence in the blood of an inhibitor of T_4-binding, would involve a similar course of events as described above, but opposite in direction. Primary alterations in serum binding lead to changes in the body distribution of hormone, but once the new equilibrium is achieved and free hormone levels are restored to normal, there are no changes in overall hormone disposal rate. This is in contrast to the effects of alterations in cellular binding.

The consequences of a primary change in *cellular* binding of hormone can be predicted from this model but, in this case, hormone metabolism and disposal as well as distribution are usually altered. An increase in net T_4-binding by cells leads to a shift of hormone from the plasma into the cellular compartment. If plasma binding is not altered, then this shift would be accompanied by a *fall* in the free T_4 level. In this case, an *increase* in the rate of T_4 supply (by thyroidal secretion) would be necessary to restore the free hormone concentration to normal. Hormone disposal rates may or may not be increased, depending on the type of cellular binding sites that are increased. If these sites are linked to enzymes that metabolize the hormone, then T_4 disposal will be augmented. This series of physiological adjustments has been observed in studies of the effect of phenobarbital on T_4 distribution and metabolism, which work will be discussed in detail in a later section of this review.

The same general model of hormone distribution, involving a partition of hormone between extracellular

binding proteins and intracellular sites, applies to T_3, in that primary alterations in the binding activity of TBG lead to corresponding increases or decreases in the circulating level of bound T_3 and (in the new steady state) an unchanged concentration of free T_3. However, because relatively little of the total T_3 pool is located in the liver, many agents that influence principally hepatic binding and metabolism of hormones exert a smaller effect on T_3 than on T_4 economy.

II. Agents That Affect Primarily Plasma Hormone Binding

A. Agents That Affect the Concentration of Plasma Binding Proteins

1. Estrogens. It has been known for many years that pregnancy increases the T_4-binding capacity of TBG (85). The observed effect of administered estrogens on serum TBG capacity (84) led to the conclusion that the TBG increase in pregnancy is due to the elevated estrogen levels. Measurements of TBG by radioimmunoasssay (198) or other direct assays (45) have confirmed that the increase in T_4-binding capacity of TBG in pregnancy or in the estrogen-treated individual of either sex is in fact due to an increase in the concentration of TBG. Oral contraceptives increase TBG levels to a degree related to the estrogen content of each preparation (156, 104). Conjugated estrogens exert similar effects on TBG levels (140). As would be predicted from the known influence of primary changes in serum binding activity, the absolute concentrations of free T_4 and free T_3 in the serum are within normal limits in pregnant women (246). TBG levels increase over a 2- to 3-week period after the start of estrogen administration (198), in keeping with a 5-day $T_{1/2}$ of TBG turnover in humans (48a). It is worth noting that high doses of sex steroids are required to obtain clear effects on TBG. There is only a small, barely significant difference in TBG levels between normal men and women (29a).

The T_4 kinetics in humans treated with estrogens (86, 347) are entirely consistent with a primary increase in serum TBG concentration and a normal free T_4 concentration: an increased circulating T_4 pool (bound T_4), a decreased fractional turnover rate (prolonged $T_{1/2}$), and an unchanged absolute T_4 turnover rate.

Estrogenic agents seem capable of altering thyroid hormone metabolism in addition to their well-known influence on serum hormone binding. Such effects are difficult to demonstrate in humans where changes in TBG predominate. Galton (109) reported that in the rat, a species without TBG, administration of estradiol causes a transient increase in T_4 deiodination rate without any change in serum T_4-binding. The effect was noted at 2 days but not at 10 days of treatment.

It has been suspected for some time that the liver is the organ responsible for the synthesis of TBG, but only recently has this been demonstrated. By use of a specific radioimmunoassay for monkey TBG, Glinoer et al. (120) measured the synthesis and secretion of this protein in isolated Rhesus monkey hepatocytes and in a line of monkey hepatocarcinoma cells maintained in culture. The same laboratory group showed that administration of β-estradiol to the animals before removal of the liver augmented the rate of synthesis and release of TBG by the hepatocytes in vitro (121). Addition of estradiol (10^{-11} M) to the medium of growing hepatocarcinoma cells stimulated TBG production 1.6-fold. In separate studies on intact monkeys, estradiol treatment had very little influence on the fractional clearance of TBG from the circulation; its major effect was to increase the absolute rate of production (synthesis) of TBG (122).

2. Androgens. High doses of androgens, in contrast to estrogens, cause a *decrease* in T_4-binding capacity of serum TBG (89, 98, 83). Free T_4 concentration remains normal (99). The effects of testosterone on T_4 distribution and disposal include an acceleration of fractional removal, a decrease in extrathyroidal T_4 pool-size, and a normal absolute turnover rate (95). An anabolic steroid, norethandrolone, has been studied in some detail. Like all androgenic agents, this steroid lowers the TBG binding capacity (and serum T_4 level), and it also increases TBPA binding capacity (31, 33). The alterations of in vivo T_4 kinetics are characteristic of those observed when binding by TBG is decreased (31). In order to separate the effects of the increased TBPA binding of T_4 from the effects of the decrease in TBG caused by norethandrolone, Braverman et al. studied T_4 kinetics in four patients whose sera were lacking TBG presumably due to a genetic trait (28). During the administration of the drug, TBPA binding capacity increased by 62%, on the average, total serum T_4 [protein-bound iodine (PBI)] increased by 33%, and the concentration of free T_4 remained normal. The fractional turnover rate of injected labeled T_4 increased slightly and the volume of distribution increased by 69%, with the result that T_4 clearance decreased in all cases. Owing to the reciprocal changes in total serum T_4 and in clearance, the calculated absolute T_4 turnover rate remained unchanged by the drug (28). In individuals with TBG, however, the effect of an anabolic-androgenic steroid on T_4 metabolism is predominantly one of a lowering of total plasma hormone binding, since TBG is more important than TBPA in overall T_4 binding.

3. Glucocorticoids. Glucocorticoids, when administered in high doses, reduce the binding of T_4 to TBG and increase binding to TBPA (326a). Oppenheimer and Werner found an average maximum decline in plasma TBG capacity (measured by electrophoresis) of 55% and a rise in TBPA capacity of 67% in five patients receiving large doses (40 to 100 mg/day) of prednisone, effects that were observed within 2 weeks of treatment (244). There was no change, however, in the net binding of T_4 by serum

(measured by equilibrium dialysis), indicating that the alterations in TBG and TBPA balanced each other. Glucocorticoids in large doses influence other aspects of thyroid hormone metabolism. Kumar et al. (185), with in vivo tracer methods that involved external monitoring, found a redistribution of T_4 away from the liver and into other tissues in a group of patients given 40 mg/day of prednisone for 5 to 7 days. In agreement with previous observations, these investigators found no net effect on overall binding of T_4 by plasma proteins, so the decrease in hepatic T_4 content that they observed probably reflected an effect on cellular binding.

4. L-Asparaginase. Garnick and Larsen (114) reported a prompt decline in the circulating level of TBG, measured both by T_4-binding activity of plasma and by radioimmunoassay of TBG, itself, in six patients given L-asparaginase therapy for acute lymphatic leukemia. From the rapidity of fall in TBG level (half-time of about 5 days), the authors concluded that TBG synthesis in the liver was completely inhibited by the initial dose of the drug. In all cases, TBG concentrations returned to pretreatment values within about 4 weeks after the last dose of L-asparaginase. The serum free T_4 concentrations changed very little during the acute decline in TBG. Heidemann, Peters, and Stubbe (141) confirmed the effect of L-asparaginase on serum TBG levels. Apparently, these rapid alterations in TBG have not been observed in patients receiving other antitumor agents.

5. Perphenazine. Earlier reports that treatment with perphenazine (Trilafon) was associated with an elevated serum PBI in some patients led some investigators (71, 235) to suggest that the phenomenon was due to an elevation in TBG. Mølholm-Hansen and Siersbaek-Nielsen (219), however, showed that, while 15% to 20% of patients receiving perphenazine, 16 to 80 mg/day (for psychosis), did indeed have abnormally elevated serum PBI values, the serum T_4 (measured by a competitive protein-binding assay) was normal in all patients and the percent of free T_4 (by dialysis) was not decreased, thereby excluding any effect of the drug on TBG concentration. The previously reported elevations in serum PBI were not explained, however.

B. Agents that Inhibit Hormone Binding to Plasma Proteins

1. 2,2 bis(chlorophenyl 4-chlorophenyl)-1,1-dichloroethane (o,p'-DDD). A drug used to treat adrenal carcinoma, 2,2-bis(2-chlorophenyl-1,1-dichloroethane (o,p'-DDD), lowered the serum PBI without producing overt hypothyroidism (76). Marshall and Tompkins (213) produced evidence that this drug competes with T_4 for binding to TBG; binding capacity of TBG was not altered in two patients treated with o,p'-DDD, but the proportion of added labeled T_4 bound to TBG was increased at the low levels of total T_4 in sera of patients. Attempts to show direct inhibition of binding by adding the drug to serum in vitro were unsuccessful owing to insolubility. The same authors pointed out the structural similarity between o,p'-DDD and T_4 (213). Two other agents with similar structural features (two phenyl rings linked to a single carbon atom), aminoglutethimide and amphenone, have not yet been tested for T_4-displacing activity.

2. Salicylate and Congeners. Salicylate is another agent that interferes with the binding of thyroid hormone to serum protein (70, 247, 304, 338, 335). Although early studies indicated that salicylate inhibits only TBPA binding, more recent work by Larsen (189) demonstrated inhibition of TBG binding, as well. Addition of sodium salicylate to human serum in concentrations frequently encountered during aspirin therapy (as an anti-inflammatory agent), i.e. at levels of 20 to 30 mg/100 ml, causes elevations in the proportions of free T_3 and free T_4 of 100% to 200% above control (189). At toxic levels (60 mg/100 ml and above) the changes were even more pronounced. Increases of this magnitude in the fraction of free T_4 cannot be attributed to inhibition of TBPA binding alone, since this protein binds only about 15% of the T_4 in human serum (337). Larsen has presented convincing evidence that salicylate competitively inhibits the binding of both T_4 and T_3 to TBG as well as to TBPA (189). In the same study, it was shown that administration of aspirin to two normal subjects for a period of 8 to 10 days, in doses sufficient to maintain plasma levels of 20 to 25 mg/100 ml, caused only slight increases in the absolute concentrations of free T_4 and T_3 (about 20% above pretreatment levels), owing to a decline in the serum concentrations of total T_4 and T_3 that nearly balanced the elevations in the fractions of free hormone (189). Although for a brief period of a day or two after the ingestion of large doses of salicylate one might find significant elevations in absolute levels of free hormone, it appears that during prolonged administration a new steady state is achieved in which the free T_4 and free T_3 levels return to normal.

Treatment with salicylates is accompanied by an acceleration of the fractional rate of T_4 turnover in humans (5). It is not clear, however, whether the effect on T_4 turnover is due to the inhibition of T_4-binding to serum proteins or to the hypermetabolic state that is a feature of salicylate treatment in large doses. Woeber and Ingbar (336) addressed this question by investigating the effects of two noncalorigenic congeners of salicylate, gentisic acid and γ-resorcylic acid, which are potent inhibitors of T_4-binding but which do not increase oxygen consumption in vivo. These investigators found that both congeners, when given to humans in doses sufficient to increase the fraction of free T_4 and to lower serum PBI to levels found during large-dose aspirin treatment, significantly increased the fractional and absolute turnover of T_4. These observations indicate that the accelerated T_4 turnover induced by salicylate is related to the inhibition of serum hormone binding and that the hypermetabolism of salicylate toxicity is probably *not* a consequence of the transient increase in free thyroid hormone levels.

Observations similar to those in humans have been made in rats. Good, Hetzel, and Hogg (124) found that both salicylate and γ-resorcylate inhibited T_4 binding to rat serum proteins in vitro and lowered serum PBI in vivo. They also found a decrease in serum thyroid-stimulating hormone (thyrotropin, TSH), measured by bioassay, that correlated with the increase in the proportion of free T_4, measured by the rate of dialysis of labeled T_4 in serum, in animals treated with either drug for 52 hr. Langer et al. (188) administered salicylate (5 to 160 mg/400 g of body weight) to rats whose extrathyroidal pool of T_4 had been labeled 16 hr previously and found an acute (within 20 min) dose-dependent decline in circulating labeled T_4.

Chopra et al. (67) recently determined the effects of salicylate administration on T_4 5′-monodeiodination in rats. After injection of 24 or 48 mg of sodium salicylate each day for 4 days into rats also given T_4 (1 μg/100 g of body weight per day) to replace endogenous T_4 secretion, serum T_4 and T_3 levels fell by 70% and 62%, respectively, at the higher dose of salicylate. Production of T_3 from T_4 in homogenates of liver from treated rats was 54% lower than in controls. Competitive inhibition of the 5′-deiodinase was demonstrated by addition of salicylate to liver homogenate. Similar findings were reported earlier for rat kidney homogenate (60). The significance of these latter findings for humans receiving therapeutic doses of salicylates is not known.

3. Fenclofenac. Recent reports indicate that the nonsteroidal anti-inflammatory drug *fenclofenac* inhibits the binding of thyroid hormones to serum proteins. Patients on long-term treatment with this drug (0.6 to 1.2 g/day) exhibit low total serum T_4 levels, to about one-third normal (163) and mild depression of total T_3 concentrations (265). Free T_4 concentrations were in the low-normal range in these cases, although the free T_4 index (calculated from a T_3-resin uptake test) was often distinctly low, despite the patients' euthyroid metabolic state (265, 218). The normal TSH levels clearly distinguish euthyroid from hypothyroid patients receiving fenclofenac (265).

4. Dinitrophenol. An agent that resembles salicylate in its effect on T_4 binding is 2,4-dinitrophenol (DNP), which inhibits T_4 binding to TBPA (338) and elevates the percent of dialyzable T_4 when added to human serum (70). The in vivo effects of DNP in rats were studied by Good et al. (124). Administration of the drug by gastric tube every 12 hr for 48 hr to a total dose 5 mg/100 g of body weight, caused a decrease in plasma PBI level to less than one-half the control value and a 2-fold or greater increase in the rate of dialysis of labeled T_4 from serum of treated animals. Simultaneously, there was a fall in bioassayable TSH in DNP-treated rats, an effect that the authors attributed to the (transient) displacement of T_4 from its binding proteins. Evidence for a direct cellular action of DNP was presented by Hillier (153), who found that addition of the drug (10^{-3} M) to fluid perfusing isolated rat liver caused a prompt 74% inhibition in deiodination of T_4. The effect occurred within 5 min after exposure to the drug and was found to a lesser degree at 10^{-4} and 10^{-5} M. The author suggested that the mechanism might involve depletion of essential cofactors (e.g. reduced [nicotinamide-adenine dinucleotide phosphate (NADP)], secondary to DNP-induced uncoupling of oxidative phosphorylation. A detailed examination of the products of iodothyronine metabolism in cultured hepatocarcinoma cells, as influenced by DNP, was made by Sorimachi and Robbins (295). They found that at 10^{-3} M in the culture medium the drug did not affect phenolic ring deiodination but did accelerate the degradation of added labeled T_4 by the cells, mainly via nonphenolic ring monodeiodination to 3,3′,5′-triiodothyronine reverse-T_3, rT_3). Nonphenolic ring deiodination of T_3 (to 3,3′-T_2) and of 3,3′-T_2 (to 3′-T_1) was also augmented slightly by DNP. The drug strongly inhibited sulfation of 3,3′-T_2 and 3′-T_1, which action may have made more of these compounds available for deiodination. Cellular uptake of the iodothyronines was unaffected by DNP in these studies.

5. Penicillin. Penicillin G, in concentrations of 10^{-3} M and higher, inhibited the binding of T_4 to human serum proteins, increasing the proportion of dialyzable T_4 when added in vitro (301). The effect principally involved prealbumin and, although reversible, it is not competitive, in that addition of increasing concentrations of nonradioactive T_4 does not abolish the penicillin-induced inhibition of prealbumin binding. In this study the doses used to demonstrate the effect were much larger than those employed clinically. In studies with an isolated, perfused rat liver system, Gorman et al. (125) showed that penicillin increased hepatic uptake of labeled T_4 from rat blood, an effect evidently analogous to the debinding phenomenon noted previously by Surks and Oppenheimer in human plasma. In addition, Gorman et al. found that the antibiotic altered the metabolism of T_4 by the liver. There was a decrease in T_4 conjugate formation and in biliary excretion of free T_4. T_4 deiodination was unaffected by penicillin. The effects on both plasma binding and hepatic disposal of T_4 in this system were obtained at penicillin G concentration as low as 2000 U/ml, a level commonly achieved in clinical practice. Nevertheless, there is no evidence that significant effects on T_4 binding occur in vivo.

6. 2,4-Dichlorophenoxy Acetic Acid (2,4-D). Another agent that alters the distribution of T_4 in vivo is the herbicide 2,4-dichlorophenoxy acetic acid (2,4-D). Florsheim et al. (105) showed that the administration of 8 mg of 2,4-D/100 g of body weight to rats for 7 days significantly lowered serum PBI. In separate experiments the same authors demonstrated an increase in the apparent total distribution volume of T_4 (determined 30 min after tracer injection) and an increase in the proportion of labeled T_4 located in the liver of 2,4-D-treated animals. In vitro competition by 2,4-D for T_4-binding

sites on serum proteins was demonstrated by dialysis, but the authors concluded that the agent is a weak competitor, since a molar ratio of 6000:1 was required to double the proportion of free T_4 (105). Whether this debinding effect is sufficient to account for the in vivo observations on T_4 distribution is uncertain.

7. Clofibrate. Ethyl ρ-chlorophenoxyisobutyrate (clofibrate, Atromid-S), a drug used in the treatment of hyperlipidemia, also alters the in vivo distribution of T_4, increasing the ratio of hepatic to serum T_4 within 3 hr after administration of the drug to rats. However, no evidence was obtained that serum binding of T_4 was altered (248). Harland and Orr (137) confirmed the acute effect of clofibrate on T_4 distribution in rats. A single injection of the drug (110 mg/300 g of body weight) caused within 4 hr a significant reduction in plasma concentration of radiothyroxine (given 24 hr previously) and an increase in hepatic radioactivity. There was also an increase in biliary content of the tracer. These acute changes are characteristic of an inhibition of serum hormone binding. The effects of chronic treatment were different. In animals given clofibrate in their diet (0.02%) for 3 weeks the level of circulating T_4 (serum PBI) was only slightly diminished as was the hepatic content of T_4. Total body T_4 disposal in these rats was unchanged. Biliary clearance of T_4 was augmented, as was fecal excretion of T_4. The normal total T_4 disposal implies a decrease in deiodinative metabolism balancing the increase in biliary-fecal disposal.

8. Halofenate. Halofenate, 2-acetoamidoethyl (*p*-chlorophenyl) (*m*-trifluoromethyl phenoxy) acetate, another drug that has been evaluated for the treatment of hyperlipidemia, inhibits binding of T_4 and T_3 to TBG (222, 79, 178). Davis et al. showed that the free acid form of this drug, the form present in plasma after oral administration, increased the percent of dialyzable T_4 when it was added to serum (79). In euthyroid patients on chronic treatment (2 to 6 weeks) with this drug, serum total T_4 levels remained unchanged but, because of the increased proportion of free hormone, the absolute free T_4 increased (79, 222). There is no evidence that the lipid-lowering effects of either clofibrate or halofenate are related to the drug-induced alterations in thyroid hormone transport.

9. Sulfonylureas. Among the sulfonylurea drugs, carbutamide is the only one with a definite antithyroid effect (see ref. 146). In contrast, tolbutamide, chlorpropamide, and acetohexamide have little or no antithyroid action but do inhibit the binding of thyroid hormones to serum proteins, both in the rat (168) and in humans (146). When added to human serum in concentrations of 12 mg/100 ml or greater, chlorpropamide produced measurable release of labeled T_3 from TBG (146). In vivo, the effects were less apparent, however. The same investigators showed that i.v. administration of 1 g of tolbutamide increased the T_3-resin uptake (an inverse measure of available binding sites in serum) by only 10%. Sulfonylureas taken orally, however, had no significant effect either on serum PBI or T_3-resin uptake (146).

10. Chlordiazepoxide and Diazepam. In a similar vein, chlordiazepoxide (Librium) and diazepam (Valium) are weak inhibitors of thyroid binding by human plasma proteins (279, 88) but neither drug has significant in vivo effects on thyroid function or on circulating levels of thyroid hormone in rabbits (88) or in humans (232, 215).

11. Heparin. Administration of heparin to humans in doses commonly employed for anticoagulation regularly causes a rise in free thyroxine concentration, primarily due to an increase in the percent of free T_4 (275, 277). This phenomenon was first reported by Hollander et al. (156), who attributed the rise in free T_4 to an elevation in serum free fatty acid levels resulting from heparin-induced activation of lipoprotein lipase activity. This explanation was particularly attractive, as addition of heparin to normal human serum failed to alter T_4-binding. However, Schatz et al. (277) presented convincing evidence that the elevation in free fatty acids could *not* account for the effect of heparin in vivo: First, the maximum increase in free T_4 occurred within 10 to 15 min after the heparin had been given i.v., earlier than the peak in fatty acid levels (30 min). Second, administration of protamine together with heparin completely prevented the rise in fatty acids but did not prevent the increase in free T_4. Third, injection of epinephrine i.v. (0.5 μg/kg) increased free fatty acid levels but had no effect at all on free T_4. In this study, single doses of heparin, from 5 to 50 mg i.v., in normal individuals resulted in a mean elevation in free T_4 (measured by equilibrium dialysis) of 250% over control (277). There were slight increases in total T_4 concentration but no change in TBG or TBPA binding capacity. Addition of heparin in vitro (5 μg/ml) had no effect on serum T_4 binding, total T_4 levels, or free T_4. Only at extremely high concentrations did heparin inhibit T_4-binding in vitro (147). Similar findings were reported by Saeed-Uz-Zafar et al. (275). In 13 patients given single doses of heparin for acute myocardial infarction, they found increases in free thyroxine concentration that averaged five times the pretreatment level and were maximal at 15 min after injection, decreasing to near control levels by 60 min. Athyreotic patients receiving T_4 replacement showed similar responses to heparin. Another anticoagulant, warfarin, had no effect on free T_4 levels. The authors (275) suggested that the acute in vivo effect of heparin might involve a transient redistribution of T_4 out of tissue stores. The smaller change (30% or less) in *total* serum T_4 noted by these and other authors (275, 147) is somewhat difficult to explain on this basis, however. Hershman et al. (147) proposed that heparin interacts with TBG to alter its binding affinity for T_4 and T_3 but direct evidence for this idea is not available. Schwartz et al. (280) studied the acute effects of heparin given in vivo on the distribution of ^{125}I T_4 between the vascular and the cellular compartments in eight human subjects. They reasoned that, since heparin administra-

tion causes a prompt increase in the percent of free T_4 in the circulation and if there were no effect of the drug on cellular T_4-binding then a rapid shift of labeled T_4 ought to occur in vivo out of the plasma into the cellular T_4 compartment. No such shift was observed in any of the eight subjects given doses of heparin sufficient to elevate the percent of free T_4 significantly. From this, the authors concluded that after in vivo administration heparin reduced T_4 binding by tissues as well as by plasma. It is not known how heparin, or more likely, a substance produced in vivo by heparin causes any of these effects. Although the mechanism is still unclear, the available evidence indicates that the in vivo administration of heparin to humans in doses commonly used for anticoagulation results in a significant but transient elevation in free T_4 concentration and, to a lesser extent, an increase in total serum T_4.

III. Agents That Alter Peripheral Thyroxine Metabolism in Vivo and in Vitro

The major metabolic pathway for T_4 is via deiodination; this accounts for about 80% of the daily T_4 degradation. The principal products are 3,5,3′-triiodothyronine (T_3), which in humans accounts for about 35%, and 3,3′,5′-triiodothyronine (reverse T_3, rT_3), which accounts for 45% (51, 61, 115, 266). The three diiodothyronines have also been identified: 3,3′-T_2 (339, 38, 41, 116), 3′5′-T_2 (42, 65), and 3,5-T_2 (206, 252); 3′-monoiodothyronine (3′-T_1) is also known (292, 323) and the totally deiodinated compound thyronine, first identified using ^{14}C-T_4 by Pittman and Chambers (254), has recently been found as an overall deiodination product of T_4, amounting to 15% to 20% of T_4 metabolites in human urine (331). Analysis was by gas chromatography and mass fragmentography. 3-T_1 has recently been characterized as a product of the monodeiodination of 3,5-T_2 (64a).

Second in quantitative importance in the disposal are the phenolic conjugates of T_4 and T_3, the glucuronides and sulfates (164); in all, these account for 15% to 20% of the thyroidal secretion of the hormones (66, 212, 230). These conjugates are hydrolyzed in the gut and excreted as T_4 and T_3 in the feces.

A minor metabolite of T_4 results from oxidative deamination and decarboxylation of the side chain: 3,5,3′,5′-tetraiodothyroacetic acid (tetrac, T_4A) (308). From earlier data, Chopra et al. (64) calculated that it represented less than 4% of the daily production rate of T_4. According to Pittman et al. (256), it represents only about 1% of the daily output of T_4.

Traces of the keto (T_3K) and lactic acid (T_3LA) analogues of T_3 have been found in rat tissues (217), but are probably not of much physiological significance. T_3K is an unstable precursor of T_3A. Tetraiodothyroformic acid (T_4F) has been found in rat liver (262).

The diphenylether bridge of the iodothyronines has generally been considered as metabolically stable in animal tissues, although it was shown some years ago by Lissitzky and Bouchilloux (201) to be broken by a mushroom polyphenoloxidase, yielding principally tyrosine and a small amount of dopa (3,4-dihydroxyphenylalanine). Plaskett (257) obtained evidence of formation of diiodotryosine in vitro from thyroxine labeled in the inner ring, a finding confirmed by Wynn and Gibbs (344). Roche et al. (267) detected tritium-labeled diiodotyrosine from doubly labeled (tritium and ^{131}I) thyroxine treated with rat liver microsomes. Rupture of the diphenylether bridge has also been demonstrated in vitro by Burger et al. (36) and by Balsam and Ingbar (11); of greater interest is the finding of traces of diiodotyrosine in vivo (12, 35a).

Of the other possible metabolites of T_4 and T_3, the decarboxylated derivatives, thyroxamine and triiodothyronamine, have not been unequivocally identified. It is worthy of comment that O-methylation of the hormones does not appear to take place, although it is a recognized, though rare, biological reaction of monohydric phenols (211); further, Maclagan and Wilkinson (209) showed that after administration of the drug n-butyl-4-hydroxy-3,5-diiodobenzoate to humans, 4-hydroxy-3,5 diiodobenzoic acid and its methyl ether appeared in the urine.

In this section, we will principally consider the effects of drugs on deiodination and conjugation of the thyroid hormones in different tissues.

A. Phenytoin and Carbamazepine

Oppenheimer et al. (237a) reported in 1961 that the serum PBI was depressed in patients receiving phenytoin (diphenylhydantoin, DPH). Because DPH displaces T_4 from TBG in vitro (243, 303, 338), it was assumed that the lowering of serum T_4 levels during in vivo administration of the drug is due solely to inhibition of plasma protein binding. However, the in vivo effects of DPH were recognized to involve more than mere binding inhibition as a result of the demonstration by Chin and Schussler (58) in 1968 that the absolute concentration of free T_4 in DPH-treated individuals was diminished. Since then, several groups, each using different methods, have confirmed this finding (220, 300, 151, 346, 50). In general, both the total T_4 and the free T_4 concentration are decreased by 15% to 30% below normal during prolonged administration of DPH. Larsen et al. (190) studied T_4 kinetics before and during DPH treatment for 9 to 14 days in five normal humans and found a 20% (average) increase in fractional disappearance rate, just about equal to the change in plasma concentration of total (and free) T_4. Thus, the absolute T_4 turnover (disposal) rate was unaltered by the drug, but because of the decrease in free T_4 level, the *free* T_4 clearance (or fractional removal rate) must have been augmented. From the measured plasma concentration of DPH and the known in vitro activity of the drug in displacing T_4 from its major binding protein, Larsen et al. (190) calculated that DPH given in vivo was nearly 10 times more effective in lowering plasma T_4 than would have been expected on the basis of its in vitro

debinding activity. This implies an effect at the cellular level. In fact, Mendoza et al. (216) had shown in 1966 that treatment of rats for 11 to 13 days with DPH induced changes in the liver that included increased uptake of radiolabeled T_4 and greater biliary output of T_4 metabolites, chiefly the glucuronide. Hamada and Nishimoto (135) studied the effects of various drugs, including DPH, on the binding of T_4 by cytosolic proteins from human liver. They found that, at concentrations of 10^{-4} M, the drug competed with T_4 for binding to at least one cytosolic protein. Because the full effects on T_4 metabolism are observed only after several days or weeks of exposure to DPH (190), suggesting that enzyme induction is necessary, it is not at all clear what role any such inhibition of cellular T_4 binding would play in this effect. A DPH-induced augmentation of T_4 disposal could explain the lowered total and free T_4 in plasma of treated humans only if the pituitary-thyroid system does not "sense" a state of thyroid hormone lack. The question of the thyroid metabolic status of DPH-treated individuals has been considered by several groups. Mølholm-Hansen et al. (220) found a small increase in basal serum TSH during DPH administration compared to values in the same subjects before treatment. However, the TSH response to thyrotropin-releasing hormone (TRH) stimulation was not altered by DPH, indicating a normal pituitary "set." Others have found basal and TRH-stimulated TSH levels to be unaltered by DPH treatment (151). By these criteria, therefore, patients receiving DPH do not appear to be hypothyroid despite the significant decrease in free T_4 concentration. Data on circulating T_3 may provide an explanation for this paradox. Total serum T_3 concentration is unaltered by DPH administration (220, 151, 346, 50) and, owing to the low T_4 level, the ratio of total T_3 to T_4 is increased by 35% on the average (50). In a preliminary report, Cullen et al. (75) described studies of T_4 and T_3 turnover before and during DPH treatment of three euthyroid humans. In two cases the rate of conversion of T_4 to T_3 was increased by the drug. This finding, if confirmed in a larger number of subjects, could explain the eumetabolic states of DPH-treated individuals in spite of the low free T_4 levels.

In the rat, treatment with DPH for 7 days (5 mg/100 g of body weight per day) lowered plasma total T_4 and free T_4 levels without altering total and free T_3 or TSH (119). In the same study, DPH administered to thyroidectomized rats maintained on T_4 replacement therapy caused a decrease in both T_4 and T_3, the T_3:T_4 ratio remaining unchanged. These authors concluded that the drug increased T_4 clearance but did not specifically stimulate 5′-monodeiodination of T_4 to T_3. Another group has found that DPH, given either as a single dose (20 mg/100 g of body weight) or chronically to thyroidectomized rats, suppresses serum TSH (7a, 307a). They postulated that DPH acts as a thyroid hormone agonist at the pituitary level.

Carbamazepine, another anticonvulsant drug, has been reported to have effects on serum thyroid hormone levels equal to those of DPH (269), but others claim that DPH is more potent than carbamazepine in this regard (346, 199). Hypothyroidism has been described in two patients during treatment with both drugs simultaneously (1), but this is probably an unusual complication that occurs only in patients with already limited thyroid reserve.

B. Phenobarbital

Phenobarbital (PB) is a drug that nicely illustrates the importance of cellular factors, in particular hepatic binding and metabolism, in thyroid hormone economy. Bernstein et al. (20) reported that hepatic accumulation of ^{125}I-T_4 was enhanced after treatment of rats with PB, 100 mg/kg per day. There was an increase both in the hepatic content of injected ^{125}I-T_4 and in the ratio of liver to plasma ^{125}I-T_4 of about 50% over control values. Liver weight increased by 30%. PB had no effect on either serum PBI or plasma binding of T_4, either in vitro or in vivo, or on the renal accumulation of ^{125}I-T_4. In the same study, these authors reported that chlordane, 25 and 75 mg/kg per day, had similar but smaller effects on hepatic ^{125}I-T_4 content compared to the alterations produced by PB. They attributed the increased hepatic uptake of T_4 in the case of both drugs to an augmentation of hepatic content of smooth endoplasmic reticulum (20). Treatment with 3,4-benzpyrene, in contrast, failed to alter either liver weight or content of ^{125}I-T_4. The same group studied the metabolism and excretion of T_4 clearance in rats given PB (237). They found a 2- to 4-fold increase in total T_4 clearance, which corresponded closely to a 2- to 5-fold increase in hepatic T_4 volume of distribution in animals treated for 5 days with PB, 100 mg/kg per day. There was a significant increase both in deiodinative metabolism, assessed by urinary radioiodide excretion, and in fecal disposal of labeled T_4 in treated rats. The latter was attributed to an augmentation both in bile flow and in the ratio of bile to plasma ^{125}I-T_4 concentration. In spite of the acceleration in T_4 turnover, serum PBI was unaffected by PB, indicating enhanced thyroidal secretion of T_4. This conclusion was supported by finding (a) an increase in thyroid/serum iodide (^{125}I) concentration and PB-^{125}I level in serum of intact PB-treated rats given ^{125}I-iodide, and (b) a fall in serum PBI after PB-treatment of thyroidectomized rats maintained on a constant dose of T_4.

In a later study, Oppenheimer et al. (241) showed that PB treatment of rats reduced the biological effectiveness of administered T_4, as measured by total-body oxygen consumption and activity of mitochondrial α-glycerophosphate dehydrogenase in liver, heart, and kidney. They concluded that PBI administration diverts T_4 away from its specific intracellular sites of action, but measurements of plasma or tissue levels of T_3 were not made in this particular study. Oppenheimer et al. compared T_4 and T_3 in terms of distribution, cellular binding, and turnover rates as influenced by PB in rats (240). It was

found that PB treatment had no significant effect on T_3 uptake by liver or on deiodinative clearance of T_3 but there was an increase in fecal clearance of T_3 by about 80% over controls, nearly as great a stimulation as that of the fecal clearance of T_4. Overall, T_3 metabolic clearance (by all routes) was increased by about 40% over controls, in contrast to a 60% increase of T_4 clearance (240). These findings are consistent with differences in distribution of T_3 and T_4: The liver accounts for nearly 30% of the total extrathyroidal cellular T_4 pool but only about 12% of the cellular T_3 pool in the rat.

In the human, as in the rat, PB administration has no measurable effect on serum binding of thyroid hormones (240, 53). Studies of T_4 and T_3 turnover and serum concentration have been made before and near the end of a 14-day period of PB administration in six patients with hyperthyroidism due to Graves' disease and in two athyreotic individuals receiving replacement doses of T_4 (53). In both groups, compensatory mechanisms involving the TSH-thyroid axis would not have been operating to obscure drug-induced changes in circulating hormone concentrations. In the hyperthyroid subjects, serum T_4 (total and free) declined during PB administration. Total T_4 (metabolic) clearance increased by 18% but fecal clearance increased by 103% during PB treatment. Similar but smaller changes were noted in both of the T_4-replaced hypothyroid patients. In regard to T_3 metabolism, only small decreases occurred in serum T_3 concentration and the overall metabolic clearance of T_3 remained unchanged during PB administration. The failure of PB to affect T_3 disposal is not surprising, since previous work had shown that the liver accounts for only a small fraction of the total T_3 pool in humans. As regards the extrathyroidal conversion of T_4 to T_3, the same authors found no effect of PB treatment on the ratio of T_3 production rate to T_4 disposal rate in an athyreotic subject receiving a constant daily dose of T_4 as replacement therapy (53).

To summarize the effects of administration of phenobarbital, the principal alterations in thyroid economy in the rat are an augmentation in hepatic uptake, cellular binding, and metabolic disposal of T_4 (by all routes) and an increase in T_3 disposal, mainly by fecal excretion. In the human, the effects of the drug appear to be limited to an increase in T_4 uptake by the liver and in disposal of T_4 via the nondeiodinative route (fecal excretion). In neither species is serum binding of thyroid hormone affected.

C. Heroin and Methadone

There have been several reports that serum T_4 and T_3 levels are higher than normal in heroin (diacetyl morphine) and methadone (6-dimethylamino-4-4-diphenyl-3-heptanone) addicts, but the cause of these rises is not clear (326, 7, 8, 155, 55); further, Jhaveri et al. (167) have demonstrated elevated T_4 and T_3 levels in infants 2 to 7 days old, born to mothers on methadone maintenance. Many of the reports on the effects of narcotics on thyroid function relate to the hypothalamic-pituitary-thyroid axis, which is outside the scope of this review. Azizi et al. (8) showed differences between T_4 metabolism during heroin addiction and during early withdrawal and in methadone-treated subjects; in the former two groups there was a marked rise in serum T_4 and T_3, sometimes into the hyperthyroid range, accompanied by a decrease in the fractional turnover of T_4. In the methadone-treated patients, the rises in serum T_4 and T_3 were less pronounced and there was no change in the fractional turnover of T_4. TBG binding was increased in all groups (see also ref. 55), so this alone could not account for the changes in T_4 metabolism. Azizi et al. suggested that these findings could be due either to decreased metabolism of T_4 in heroin addiction or increased hepatic metabolism of T_4 during methadone treatment. As pointed out by Ho et al. (155), interpretation of metabolic data in drug addicts is complicated by the fact that many of them have taken more than one drug, and the drugs themselves are often grossly impure and adulterated by unknown compounds. Another factor so often present in these patients is viral hepatitis, which alters many parameters of thyroid function.

D. Methylphenidate

The psychotropic drug methylphenidate (Ritalin) lowers serum T_4 and T_3 levels when administered acutely or chronically (21 days) to intact rats (127). In T_4-maintained thyroidectomized rats, there was also a fall in serum T_4, which must reflect enhanced T_4 turnover. Further, the serum levels of T_4 and T_3 in the thyroidectomized Ritalin-treated rats were lower than in the intact animals, indicating that the thyroids in the intact group were compensating for the increased T_4 turnover by increasing thyroidal hormone secretion. The drug did not affect thyroid hormone metabolism in six hyperactive children receiving ritalin therapy.

E. Carcinogens

The effects of 3-methylcholanthrene (MCA) were investigated in 50-day-old female rats that had been injected with ^{131}I-T_4 daily for 17 days in order to label the T_4 pool to equilibrium (229). Administration of MCA, 10 mg/day for 10 days by intragastric tube, profoundly altered the pattern of T_4 metabolism: Approximately 70% of the daily dose of ^{131}I-T_4 was excreted in the feces, compared to only 40% in control animals. The serum PB-^{131}I was reduced to about one-half of the controls in MCA-treated rats. The authors suggested that MCA caused an increase in the rate of hepatic conjugation of T_4, thereby leading to increased fecal disposal and depletion of circulating T_4.

Goldstein and Taurog (123) administered 3,4-benzpyrene to rats in a single injection and found a 3- to 4-fold increase in biliary excretion (via a cannula in the bile duct) of labeled thyroxine, either exogenously adminis-

tered or endogenously produced. Almost all of the excess T_4 in bile could be accounted for by enhanced excretion of the glucuronide conjugate. Bile flow was not altered. The effect on T_4 glucuronide excretion could not be demonstrated at 9.5 hr after the drug was administered, from which the authors concluded that drug-induced displacement of T_4 from its binding proteins in plasma was not the mechanism involved. In the same study, the formation of T_4 conjugates by liver slices and homogenates was examined. Liver preparations from benzpyrene-treated rats showed a several-fold increase in capacity to form glucuronides, best explained by postulating an increase in the level of hepatic glucuronyl transferase. The authors compared the effects of phenobarbital (50 mg/kg per day for 5 days) with those of benzpyrene and discovered that PB augmented bile flow and increased T_4 excretion by this route by only 50% over controls, much less than the effect of benzpyrene. Furthermore, in the PB-treated rats there was no change in the capacity of liver homogenates to form T_4 glucuronide. The PB-stimulated excretion of T_4 was attributed largely to an increase in bile flow.

Bastomsky (14) compared the effects of dichlorodiphenyl trichloroethane (DDT) and polychlorinated biphenyls (PCB) on T_4 metabolism in rats. Rats given 25 mg of DDT per kg i.p. for 4 days showed no significant change in biliary excretion of injected ^{125}I-labeled T_4 (as percent of dose), but there was an increase in bile flow, a slight elevation of the bile-to-plasma ^{125}I-T_4 ratio, and thus an increase in the biliary clearance of ^{125}I-T_4. The proportion of total biliary ^{125}I as T_4 glucuronide was slightly increased by DDT, but there was no effect on serum PBI. In contrast, PCB (25 mg/kg a day for 4 days) caused a 4- to 5-fold increase in the 3-hr biliary excretion of ^{125}I-T_4, a marked increase in the bile-to-plasma T_4 ratio, and a modest increase in bile flow. There was a significantly greater fraction of biliary ^{125}I present as T_4-glucuronide in PCB-treated animals. In addition to these effects on biliary disposal of T_4, PCB inhibited T_4 binding to plasma protein, as evidenced by an increased resin uptake of labeled T_3 after in vitro addition of PCB to rat serum or after administration in vivo. The serum PBI was significantly reduced by PCB administration, probably as a consequence of both the inhibition of hormone binding by plasma proteins and the augmented hepatic metabolism and biliary excretion of T_4. Evidence that the latter effect involved induction of hepatic glucuronyl transferase was provided by subsequent studies by Bastomsky and Murthy (15). They found that administration of PCB, either by cutaneous application or by feeding for 4 days, increased in vitro glucuronidation of T_4 by 10,000 $\times$ *g* supernatant fractions of liver homogenates, whether the activity was based on protein concentration of the supernatant fraction or on total liver weight. In this respect, PCB is similar to other inducers of hepatic T_4-conjugating activity, benzpyrene and methylcholanthrene.

F. Butyl-4-hydroxy-3,5-diiodobenzoate (BHDB)

A structural analog of T_4, butyl-4-hydroxy-3,5-diiodobenzoate (BHDB), first received considerable attention three decades ago because of its apparent anti-T_4 activity. This compound was found to inhibit the effect of T_4 on the induction of amphibian metamorphosis (107) and on the stimulation of oxygen consumption in mice (208, 283). Early work indicated that BHDB interfered with the deiodination of T_4 in vivo (152, 330, 313) and in vitro in rat liver extracts (207) and slices (345). However, in the latter in vitro studies, which were performed before newer methods of investigating deiodination became available, products of T_4 deiodination other than iodide were not identified, and so the relationship of these aerobic reactions to the specific monodeiodination of T_4 is not clear. Van Arsdel and Williams (313) showed that BHDB-treatment of rats speeded the removal of labeled T_4 from plasma and increased hepatic uptake and fecal excretion of T_4. A number of groups have shown that BHDB interferes with the binding of T_4 to serum proteins (145, 165), but it would appear to be a relatively weak inhibitor, since concentrations of BHDB of the order of 10^{-4} M or greater are needed to show an effect in vitro.

A detailed study of the effects of BHDB on T_4 and T_3 metabolism was carried out by Escobar del Rey and Morreale de Escobar (91). They used thyroidectomized rats maintained either on 3 μg of ^{131}I-T_4 or 0.5 μg of ^{131}I-T_3 per day in order to obtain isotopically equilibrated hormone pools. After 7 days on this regime, rats were fed 25 mg of BHDB per day in the diet. Within 24 hr after starting administration of the drug, the fecal excretion of ^{131}I-T_4 increased nearly 2-fold. After 2 to 3 days on BHDB, the fecal ^{131}I-T_4 excretion returned nearly to the control level. The pattern of urinary ^{131}I (as iodide) excretion was opposite in direction; the fall in urinary ^{131}I (reflecting a decrease in deiodination of T_4) occurred slightly later than and was less marked than the alteration in fecal disposal of T_4. The changes in T_3 disposal and deiodination resulting from BHDB feeding were qualitatively similar to the pattern of changes in T_4 metabolism but of lesser magnitude. In addition a "rebound" effect was noted in T_3 excretion after the fourth day of drug administration. The authors proposed that the primary effect of BHDB is an acute alteration in the availability of thyroid hormone to the tissues, involving an increase in hormone concentration at those sites in the liver that govern conjugation and biliary excretion. Secondary to the depletion of hormone from extrahepatic tissues and those hepatic sites linked to deiodination, there is a decrease in total-body deiodination of hormone. They suggested that the inhibition of plasma hormone-binding might be responsible for at least some of the acute effects of the drug, i.e. an increase in the (hepatic) cell to plasma ratio of hormone. Drug-induced alterations of hormone distribution within the liver cell are also a possibility.

Detailed studies of the products of hepatic metabolism of T_4 and its analogs were performed by Flock and associates, who found that BHDB-feeding of rats caused stimulation of the conjugation of ^{131}I labeled T_4, tetrac, 3,5,3′-triiodothyroacetic acid (triac), and the propionic acid derivatives of T_4 and T_3, and an increase in the biliary excretion of all of these conjugates. At the same time, deiodination (phenolic ring) of these tracers was decreased (102). In a later study, the same group (103) examined T_4 metabolism in the Gunn rat, a strain with a genetic absence of bilirubin glucuronyl transferase, and found that the biliary excretion of ^{131}I after injection of ^{131}I-T_4 was about one-half that of normal rats. Of this only about 1% of biliary ^{131}I was in the form of T_4-glucuronide in the Gunn rat, in contrast to 41% in other strains, the remainder of the radioiodine being in the form of iodide and sulfoconjugates of T_4 and its products. Administration of BHDB to the Gunn rats increased total biliary ^{131}I output to a mean of 41% of the administered dose of ^{131}I in 24 hr, in contrast to 11% in untreated Gunn rats, the proportion as T_4-glucuronide increasing to only 2% of biliary ^{131}I in the BHDB-treated Gunn animals. In both types of rats, BHDB decreased the deiodination of labeled T_4. More recent work by Iwasa et al. (165) demonstrated that in rats BHDB (0.05% in diet) lowered plasma T_4 and T_3 concentrations but did not produce goiter or elevate TSH levels. They confirmed the increase in fecal excretion of T_4 and showed that the drug inhibits binding of T_4 to plasma proteins. In addition, thyroidal radioiodide uptake was depressed to extremely low levels, but the authors attributed this to iodide released by deiodination of BHDB itself.

The available evidence strongly suggests that BHDB exerts an effect directly on the hepatic cell either to cause a redistribution of T_4 from deiodinating enzyme to sites active in conjugating the hormone or to induce an increase in T_4 conjugating activity. It seems unlikely that the observed enhancement in conjugation and biliary excretion of hormones due to BHDB could be explained simply on the basis of its inhibitory effect on serum hormone binding. The latter mechanism, however, may play a role in the first minutes or hours after administration of the compound.

Nakamura et al. (225a) have recently described the effects of β-diethylaminoethyl-2,2-diphenylpentanoate (SKF 525-A, proadifen), an inhibitor of hepatic drug metabolism. In vitro, the drug inhibited the oxygen-dependent deiodination of T_4 by rat liver slices but had little effect on T_3 formation, which is a reductive step. Its effects in vivo were more complicated. When given either as a single dose (3.5 mg/100 g of body weight) or in repeated injections (1.8 mg/100 g of body weight, twice daily), SKF 525-A increased the metabolic clearance of T_4 by both fecal and urinary (deiodinative) routes. The former pathway was augmented to a greater extent. The authors (225a) showed that the drug inhibited the serum binding of T_4, and they attributed its in vivo effects, at least in part, to this action. They also postulated a direct effect on hepatic mechanisms of T_4 disposal, pointing out the qualitative similarities in the actions of this drug and those of BHDB.

G. Antithyroid Drugs

1. Effects in Vivo. It has long been recognized that certain antithyroid drugs have an action that cannot be accounted for solely in terms of their effect on thyroid hormone synthesis in the thyroid gland. This was first seen when thiouracil and its derivatives were found to require twice the amount of T_4 to reverse their effect in the goiter prevention assay compared with other drugs such as the mercaptoimidazoles. In the late 1940s, before the discovery of T_3 (130), no obvious reason for these anomalous results could be found, and it was not until the unequivocal demonstration of the conversion of T_4 to T_3 in man (32, 255) that the hypothesis that thiouracils inhibit the peripheral conversion of T_4 to the more active hormone had a rational basis. Early work in this field has already been fully reviewed (224, 223). In this article attention will be principally focussed on the formation of metabolites of T_4 revealed by newer methods of radioimmunoassay and on the biochemical mechanisms involved (see below). Propylthiouracil has been the drug most studied and there is general agreement that it does interfere with T_4 conversion to T_3; at the same time, a rise in the biologically inactive rT_3 has been shown to occur. These changes have led to the suggestion that propylthiouracil (PTU) may have an "antithyroid" action at the peripheral level too. A summary of these reports is shown in table 1.

That PTU also inhibits the deiodination of T_3 was shown in 1962 by Braverman and Ingbar (30) and by Morreale de Escobar and Escobar del Rey (223a). Later reports by others have confirmed this finding (239, 108, 143). Heinen et al. (143), who studied the deiodination of T_3 by rat liver enzymes, found the reaction so markedly inhibited by PTU that they concluded that the best antithyroid therapy in hyperthyroidism was that which did not interfere with T_3 deiodination.

Three reports have appeared on the effect of PTU on serum rT_3 and on 3,3′-diiodothyronine (3,3′-T_2). Hüfner and Grussendorf (158) studied the effect of oral PTU (650 mg at three 7-day intervals) in two euthyroid subjects, and demonstrated a rapid rise in plasma rT_3 after each dose of PTU, reaching 100% above the control level; there was a corresponding rapid but less spectacular rise in plasma 3,3′-T_2, reaching about 50% above the control level. Laurberg and Weeke (194) infused rT_3 into hyperthyroid patients on PTU or 1-methyl-2-mercaptoimidazole (MMI) therapy. During treatment, serum T_4 and T_3 levels slowly fell, but those of T_3 were lower, as expected, in the PTU-treated compared with the MMI-treated patients. Somewhat surprisingly, during rT_3 infusion, serum 3,3′-T_2 values increased concomitantly with rT_3 whichever antithyroid treatment was given. This is con-

TABLE 1

*Effect of 6-propylthiouracil on serum T_4 and its derivatives in different thyroid states**

Species	Thyroid Status	Total Daily Dose (mg)	Duration of Treatment	T_4	T_3	rT_3	Ref.
Man	Tox.	800	5 days	↓Slight	↓(55)		2
Man	H-T_4	1000	7 days	No change	↓(26)		272
Man	H-T_4	1000	8 days	No change	↓(31)		117
Man	Tox.	100–1200 (+Iˉ)	8 days	↑(24)	↓(50)	↑Temp.	74
Man	H-T_4	1000	7 days	No change	↓	↑	174
Man	Eu.	600	5 days		↓(16) Temp.	↑(100)	328
Man	H-T_4	800	1–2 wk.		↓(12)	↑(13)	285
Man	Tox.	600	5 days	↓Slow	↓(50)	↑(57)	193
Rat		0.1% In drinking water	3.5–8 wk.		↓(>40)		239
Rat	H-T_4	1 mg, 2 times	2 days	↑(N.S.)	↓(50)		19
Rat	H-T_4	1 mg/100 g of body wt.	5 days	↑(12)	↓(49)		108
Rat	H-T_4	1 mg/100 g of body wt.	13 days	↑(40)	↓(50)		191

* Numbers in parentheses refer to percentage of change after treatment, to the nearest whole number. Abbreviations used are: Eu., euthyroid; Tox., thyrotoxic; H-T_4, hypothyroid on T_4 therapy; N.S., not significant; Temp., temporary.

trary to the usual finding, that MMI does not affect the peripheral metabolism of the iodothyronines (see ref. 174). However, when antithyroid treatment was stopped, the serum level of 3,3′-T_2 fell more slowly in the PTU-treated than in the MMI-treated patients, suggesting that PTU may have had some inhibitory action on 3,3′-T_2 degradation. A brief report by Ködding and Höffken (183) describes the effects of PTU (up to 200 mg/day) and MMI (up to 120 mg/day) on rT_3 and 3,3′-T_2 serum levels in hyperthyroid patients. Serum T_4 and T_3 *fell* during both treatments, as did rT_3 and 3,3′-T_2. These data conflict with the general view that T_3 and rT_3 vary reciprocally under the influence of PTU; the fall in T_2 is also contrary to previous findings; these discrepancies cannot at present be explained. Nevertheless, it would appear that PTU interferes with 5′-monodeiodination of all iodothyronine compounds so far examined, though the effect may vary in extent for different compounds.

In the rat, the biliary and fecal pathways of thyroid hormone disposal are considerably greater than in man (315, 271, 66), and PTU has been shown to affect these pathways in the rat, though not so far in man. Van Arsdel and Williams (313) showed that parenteral administration of PTU (10 mg every 12 hr) in adult rats markedly increased the fecal excretion of nanogram doses of ^{131}I-T_4 and ^{131}I-T_3; PTU was also found to double the biliary secretion rate of labeled T_4. These findings were confirmed and extended by Lang and Premachandra (187), who showed that in PTU treated rats the rates of biliary secretion of labeled T_4 and T_3 rose 186% and 180%, respectively, above the control values. They futher showed that the changes in hepatic clearance occurred before any effect on hormonal deiodination was demonstrable, from which they concluded that these effects of PTU are independent of each other.

Kot and Klitgaard (184) were unable to demonstrate any effect of thiouracil (TU) on the biliary secretion of ^{14}C-T_4 given parenterally to rats in very large doses (78 μg/100 g of body weight). Whether the high dose level used in these experiments was responsible for the discrepancies between these and the above findings (313, 187) is not clear; Galton and Nisula (112) found that with increasing doses of T_4 up to 20 μg/100 g of body weight per day in ^{131}I-T_4-treated rats, the serum and urinary levels of radioactivity tended to plateau, whereas biliary and fecal clearances appeared to be unlimited.

2. Effects in Vitro. The 5′-deiodination of T_4 (conversion to T_3) has been demonstrated in vitro with a large number of different tissue preparations: rat kidney slices (3a), rat liver slices (128, 10), homogenates of rat liver (132, 320, 148a, 159, 62, 176), rat kidney homogenates (59, 60, 62), cultured human liver and kidney cells (298a), human leucocytes (334), human fibroblasts (265a), human thyroid cells (20a), rat thyroid slices (134, 129), and thyroid subcellular particulate fractions (90). Recent studies have provided evidence that this reaction also occurs in the pituitary (56, 173) and brain (177).

Subcellular fractionation studies indicate that in the liver T_4 5′-deiodinase activity is localized to microsomes (148a, 97). Characteristics of the hepatic system include a pH optimum of 6 to 6.5, inactivation by heat and oxidizing agents, and dependence on thiol compounds (reduced glutathione, mercaptoethanol, or dithiothreitol) (63, 172, 319, 320). These latter observations indicate that the active site of the enzyme includes one or more cysteine residues. The reaction in liver homogenates is inhibited by sodium azide, calcium chloride, mercury compounds, tertbutylhydroperoxide, TU and PTU, oral cholecystographic agents, salicylates, and propranolol. PTU was the most potent of these inhibitors; 50% inhibition was induced by 5 μM PTU (62). Detailed studies of the mechanism of PTU inhibition of 5′-deiodination by Leonard and Rosenberg (196, 197) in crude membrane fractions of rat kidney led these workers to postulate that PTU forms a mixed disulfide with catalytically important thiol(s) on the enzyme. The evidence upon which they based this idea includes the following observations: (a) The inhibitory effect of PTU can be prevented or reversed by high concentrations of dithiothreitol (DTT), methimazole, or thiourea. (b) The extent of inhibition is

greatest when the enzyme is exposed to PTU under conditions of high catalytic activity, i.e. greater in the presence of T_4 than in the absence of T_4. (c) Inhibition is persistent and does not require the continued presence of PTU. (d) The inhibition by PTU of 5′-deiodinase activity in liver (62) and kidney (60) is uncompetitive with respect to substrate (T_4) and competitive with respect to thiols (196). (e) Finally, the latter workers found that ^{35}S-labeled TU binds to crude deoxycholate-solubilized 5′-deiodinase preparations of kidney. The formation of bound ^{35}S was increased by incubation of the enzyme preparation with T_4 and decreased by MMI. Treatment with DTT released nearly half of the bound ^{35}S, which was identified as free TU.

A resemblance of the properties of 5′-deiodination of T_4 to those of the enzymatic and chemical dehalogenation of 5-bromo- and 5-iodo-2′-deoxyuridylate (325a) led Visser (319) to propose the following model of 5′-deiodination of T_4: The primary event is an attack by a nucleophile of the enzyme, e.g. a thiol group, at the 2′ or 6′ position of T_4, yielding the 2′,3′-dihydro derivative. Removal of the 3′- or 5′-iodine occurs with oxidation of the thiol group of the cofactor and regeneration of the active enzyme.

In the model that has been put forward by Leonard and Rosenberg (197), the T_4 5′-deiodinase exists in two functional states, thiol-reduced and thiol-oxidized. Only the former is catalytically active in 5′-deiodination, in the process of which the enzyme-thiol is oxidized. The latter requires a thiol cofactor, such as reduced glutathione, to become reduced to the active form. In this model, thiol cofactor is consumed (oxidized) and can be considered a second substrate. PTU forms a mixed disulfide only with the oxidized thiol group of the enzyme, which would account for the finding that PTU-inhibition is enhanced by T_4 (substrate) utilization. The much greater potency of PTU as an inhibitor of 5′-deiodination compared to methimazole or thiourea is explained by the greater stability of the PTU-mixed disulfide. A variety of thiols and thioureylenes (including methimazole and thiourea) are capable of cleaving the PTU-enzyme disulfide, thereby regenerating the catalytically active thiol form of the enzyme (196, 197). In the absence of PTU, neither methimazole nor thiourea in concentrations as high as 1 mM affect enzyme activity.

Evidence from studies of enzyme kinetics indicates that the same 5′-deiodinase converts rT_3 to 3,3′-T_2: The 5′-deiodination of T_4 is inhibited by rT_3 in a competitive manner (62). The K_m for rT_3 (as substrate) in the rat liver microsomal system is much lower than the K_m for T_4 and the V_{max} is nearly five times higher (322).

Recent attempts to solubilize the 5′-deiodinase have met with some success. Leonard and Rosenberg (197a) treated a crude membrane preparation of rat kidney with sodium deoxycholate or phospholipase A_2. The solubilized activity was restored and protected from inactivation by soybean phospholipid, which appeared to form a macromolecular complex containing the enzyme. During these manipulations, T_4 to T_3 activity paralleled rT_3 to 3,3′-T_2 activity, providing further evidence that the same enzyme catalyzes 5′-deiodination of both T_4 and rT_3.

Monodeiodination of T_4 in the tyrosyl ring (5-deiodination) yields rT_3. Although this reaction has not been studied as thoroughly as 5′-deiodination, several points of difference are apparent. The pH optimum of 5-deiodination of T_4 is higher (approximately 8.0) in homogenates or subcellular fractions of liver (49, 155a, 66, 321) and kidney (114a). The 5-deiodination reaction has been demonstrated in a line of monkey hepatocarcinoma cells (295), in human leucocytes (334), and in rat brain (306). Both T_4 and T_3 are substrates for 5-deiodinase, the latter being converted to 3,3′-T_2. Like the 5′-deiodinase, it is thiol-sensitive and is inhibited by PTU but not by methimazole (49). The 5-deiodinase of liver is present mostly in the microsomal fraction (97), but under certain conditions of homogenization and subcellular fractionation, 5-deiodinase activity has been recovered in the soluble fraction with little or no 5′-deiodinase activity (49). The 5-deiodinase activity is slightly more stable during storage and exposure to aerobic conditions in the absence of thiols (97).

There is some difference of opinion regarding the relative potency of PTU as an inhibitor of the two deiodinase systems. Hüfner and Grussendorf (158a) reported that PTU inhibits 5′-deiodination and 5-deiodination equally. On the other hand, Chopra et al. (66), who also studied liver homogenate, found that PTU was a more effective inhibitor of rT_3 to 3,3′-T_2 (5′-deiodination) than of T_3 to 3,3′-T_2 (5-deiodination). Woeber (334), who worked with human leucocytes, also found PTU to be more potent in inhibiting 5′-deiodination (T_4 to T_3) than 5-deiodination (T_4 to rT_3). The in vivo effects of PTU tend to support the latter findings, in that serum rT_3 levels rise (mainly due to impaired deiodination to 3,3′-T_2) and T_3 concentration falls (due to inhibition of T_4 to T_3). The specific reactions in which effects of PTU have been described are summarized in table 2.

Of all the tissues studied to date, the pituitary appears to be unique in that the 5′-deiodination of T_4 in this tissue is uninfluenced by PTU, either in vivo (287, 56) or in vitro (177). The reason for this property of the pituitary enzyme is not apparent, but the extraordinary dependence of 5′-deiodination on relatively high concentrations of thiol compounds (100 mM DTT for maximal activity) might be a factor.

H. Propranolol

The association of β-adrenergic stimulation and hyperthyroidism has been recognized for many years (343, 34). The first attempt to study the effect of a β-blocking drug in hyperthyroidism was made by Leak (195) in a patient with malignant exophthalmos; he used guanethidine, working up from 10 to 90 mg/day, and noted decreased tachycardia and tremor and a fall in basal

TABLE 2
Effect of propylthiouracil (PTU) on iodothyronine deiodination in vitro

Tissue	Preparation	Reaction	Ref.
Inhibition by PTU demonstrated			
Liver (rat)	Slice	$T_4 \rightarrow T_3$	128,10
	Homogenate	$T_4 \rightarrow T_3$	320,62
		$T_4 \rightarrow T_3$; rT_3 degraded.	176
		$T_4 \rightarrow T_2$	158a
		$T_4 \rightarrow rT_3$	49
		$T_3 \rightarrow T_2$; $rT_3 \rightarrow T_2$	69
	Perfused in situ	$T_4 \rightarrow T_3$	166
Liver (monkey)	Cells (hepatoma)	$T_3 \rightarrow T_2$; $rT_3 \rightarrow T_2$	296
Kidney (rat)	Homogenate	$T_4 \rightarrow T_3$	59,60
	Membranes	$T_4 \rightarrow T_3$	196,197
Thyroid (rat)	Hemilobes	$T_4 \rightarrow T_3$	129
	Mince	$T_4 \rightarrow T_3$	134
	Subcellular particulate	$T_4 \rightarrow T_3$	90
Thyroid (dog)	Perfused in situ	$T_4 \rightarrow T_3$; $T_4 \rightarrow rT_3$	192
Leucocytes (human)		$T_4 \rightarrow T_3$; $T_4 \rightarrow rT_3$	334
No effect of PTU demonstrated			
Pituitary (rat)	Homogenate	$T_4 \rightarrow T_3$	173

metabolic rate (BMR) from +60% to +20%. Guanethidine had no effect on eye signs, weight, butanol-extractable iodine, or plasma cholesterol, and the patient was made euthyroid with methylthiouracil.

Propranolol has been used for more than 12 years in the treatment of hyperthyroid patients awaiting surgery or other therapy (133, 282) and is now commonly used as an adjunct in the treatment of hyperthyroidism. Like guanethidine, its immediate effects are reduced tachycardia, tremor, sweating, and palpitations and, also like guanethidine, it does not affect the course of the disease.

Besides its β-blocking action, propranolol inhibits the peripheral conversion of T_4 to T_3; this is in contrast to other similar drugs, e.g. practolol, that alleviate the symptoms of hyperthyroidism without affecting the peripheral metabolism of T_4 (225). In general, serum levels of T_4 are little affected by propranolol treatment but serum T_3 levels are generally lowered and rT_3 is elevated to a considerable extent. Faber et al. (93) have recently shown that in euthyroid subjects receiving 20 mg of propranolol four times a day, serum 3′,5′-T_2 was also elevated, but the maximum rise in rT_3 and T_2 did not coincide with the fall in T_3; it occurred 3 to 4 days after the start of treatment, whereas the decrease in T_3 did not reach a significant level before 7 days had elapsed. In this study, serum 3,3′-T_2 levels did not change, but in an earlier one by the same group (204), propranolol lowered serum 3,3′-T_2 levels in parallel with serum T_3. The findings of a number of authors presented in table 3 show that there is a considerable variation in the magnitude of serum T_3 decrease, not related to the dose of propranolol. For instance, 80 mg of propranolol per day produced a significant fall in serum T_3 according to Nauman et al. (228), Theilade et al. (307), and Lumholtz et al. (203, 205) but was without effect according to Heim et al. (142); larger doses (160 to 320 mg/day) did not produce greater reductions in serum T_3. These variations may in part be due to difference in individual handling of the drug: It has been shown by Feely et al. (96) that in 15 hyperthyroid patients receiving 40 mg of oral propranolol every 6 hr the plasma levels of the drug ranged from about 5 to 100 μg/liter, 4 hr after the dose.

It is to be noted that when serum T_3 measurements are made consecutively after administration of propranolol, the first value may be higher than subsequent ones (225, 307), indicating an "escape" from the propranolol effect. In this connection, it is interesting to note that Wartofsky et al. (325) demonstrated a decrease in T_4 turnover in propranolol-treated hyperthyroid patients (40 mg six times a day for 5 days) from 20.4 ± 2.7%/day to 14.0 ± 1.2%/day, and that this decrease continued to 8.5 ± 2.2%/day, 5 days after cessation of treatment, whence they concluded that propranolol was not the causative agent in reduced T_4 metabolism.

There is general agreement that the alleviation of thyrotoxic manifestations by propranolol is not due to any effects on T_4 metabolism. An interesting dissociation between the β-blocking action of propranolol and its effect on T_4 metabolism has been shown by Heyma et al. (150); these authors treated six hypothyroid patients receiving T_4 replacement therapy with D-propranolol (80 mg twice a day), which has no β-blocking activity, and found no change in pulse rate or blood pressure but a significant fall in serum T_3 and in the T_3:T_4 ratio, though there was no change in serum T_4. Similarly in euthyroid subjects receiving 200 μg of T_4 per day, D-propranolol produced no significant change in serum T_4 but a decrease in serum T_3 (−15%) and a fall in serum T_3:T_4 ratio.

These authors (150) have also shown that DL-, L-, and D-propranolol all inhibited the conversion of T_4 to T_3 by isolated rat renal tubules at 200 μM concentrations and that quinidine had the same action, suggesting that the T_4-deiodinating system is inhibited by propranolol by a "membrane-stabilizing" action; further, the β-blockers sotalol and atenolol, which do not possess membrane-stabilizing activity, were without effect on T_4 deiodination.

The effect of propranolol on liver T_4 deiodinase in rats is unclear; Tal et al. (305) injected groups of intact rats with 1, 3, and 5 mg of propranolol/kg i.p. with the following results: the 1-mg dose had no effect on serum T_4; after the 3-mg dose the serum T_4 rose to 240% of the control value, and after the 5-mg dose, to 280%. In hypophysectomised rats, the increases in serum T_4 were even greater, reaching nearly 500% with the highest dose of propranolol. On the other hand, Azizi et al. (8), after

TABLE 3

*Effect of DL-propranolol on serum T_4, T_3, and rT_3 in different thyroid states in humans**

Thyroid Status	Total Daily Dose (mg)	Duration of Treatment	T_4	T_3	rT_3	Ref.
Eu.	120–160	3 days	↑(7)			333
Tox.	80	10–12 days	No change	↓(22)		228
Tox.	80	3 mo.	No change	No change		214
Tox.	240	2–4 wk.	↑ Slight	↓(30)		225
Tox.	80	7 days	No change	↓(20)	↑(16)	307
Tox.	160	2 wk.	↑(15)	↓(6)		139
Tox.	320	2 wk.	No change	↓(20)	↑(41)	317
Tox.	80–160	1–2 wk.	No change	↓(30)		329
H-T_4	80–160	1–2 wk.	↑(8)	↓(30)		329
Tox.	40	3–4 hr.	No change	↓(44)		202
Eu.	40	3–4 hr.	No change	↓(50)		202
H-T_4	80	1 wk.	No change	↓(13)		205
Tox.	120	6 wk.	No change	↓(15)	↑(34)	171
Tox.	160	1 wk.	No change	↓(18)	↑N.S.	276
Eu.	220	6 days	No change	↓		169
Tox.	80	2 wk.	No change	No change		142
Eu.	80	2 wk.	No change	No change		142
Tox.	80	1 wk.	No change	↓	↑	92
Eu.	80	1 wk.	No change	↓	↑	92
H-T_4	80	1 wk.	No change	↓	↑	92
Eu.	160	2 wk.	No change	↓(22)		150
Tox.	160	10 days	No change	↓(27)		168

* Numbers in parentheses refer to percentage of change after treatment, to the nearest whole number. Abbreviations used are: Eu., euthyroid; Tox., thyrotoxic; H-T_4, hypothyroid on T_4 therapy; N.S., not significant.

i.p. injections of between 5 and 20 mg/kg in rats, found no change in serum T_4 or in the peripheral metabolism of ^{125}I-T_4. This negative finding in rats was supported by the data of Goulding et al. (126). Jurney et al. (169a) administered propranolol by constant infusion into Wistar rats, varying the dose to achieve serum levels of the drug ranging from 27 to 237 ng/ml. Above 125 mg/ml, both serum T_4 and T_3 concentrations decreased, but free hormone levels remained unchanged. Similar findings were obtained in T_4-replaced thyroidectomized rats, so a direct effect on thyroidal secretion was unlikely. Van Noorden et al. (316) found that propranolol in very large doses (580 and 1160 μM) inhibited the conversion of T_4 to T_3 by rat liver parenchymal cells in vitro; 290 μM propranolol was ineffective; these doses are approximately three to six times greater than those found effective by Heyma et al. (149) in isolated kidney parenchymal cells.

I. Glucocorticoids and Stress

1. Glucocorticoids. For early work on the effects of adrenocorticotropic hormone (ACTH), adrenal steroids, and stress on thyroid function, the reader is referred to reviews by Money (221) and by Ingbar and Freinkel (162). This latter work principally described direct effects on the thyroid, renal clearance of iodide, and changes in the T_4-binding serum proteins (244). Cortisone was not thought to have much effect on T_4 metabolism in man (161). The first demonstration of a direct action of cortisone on T_4 metabolism was made by Bondy and Hagewood (26); they showed that it retarded the rate of removal of T_4 (PBI) from the serum of thyroidectomized, T_4-maintained rats. Blomstedt and Einhorn (23) later showed that large doses of cortisone decreased the slope of ^{131}I-T_4 disappearance in the serum of euthyroid men and Kumar et al. (185) found that prednisone retarded the disappearance of ^{131}I-T_4 in normal, hyperthyroid, and treated hypothyroid subjects. Subsequent work has shown that the corticosteroids do not greatly influence the rate of metabolism of T_4 in euthyroid adult humans although they do lower serum T_4 values in thyrotoxic patients. Nevertheless, Gamstedt et al. (112a) have shown that in euthyroid subjects given graded daily oral doses (1.5, 3.0, 4.5, and 6.0 mg) of β-methasone for 5 days, the fall in both serum T_4 and T_3 was related to the dose; this was not the case for rT_3. The principal action of glucocorticoids appears to be an inhibition of the conversion of T_4 to T_3 and a slowing of rT_3 breakdown. The mechanism of these reactions is not clear but it has been suggested (68) that glucocorticoids may selectively inhibit the 5′-deiodinase, while not affecting or possibly stimulating the 5-deiodinase. These findings have been summarized in table 4. Bános et al. (12a) have recently shown that enhancement of endogenous glucocorticoid secretion by ACTH administration to euthyroid and hyperthyroid women caused an increase in serum rT_3 values that was always greater than the corresponding fall in serum T_3.

A different pathway of T_4 deiodination is shown in the data of Osathanondh et al. (245) in human neonates; administration of dexamethasone to mothers a few hours before delivery by caesarian section resulted in large rises in both T_3 and rT_3 in cord blood although T_4 and TSH values remained unchanged. The authors suggested that

TABLE 4
*Effect of glucocorticoids on T_4, T_3, and rT_3 in plasma**

Species	Thyroid Status	Drug	T_4	T_3	rT_3	Ref.
Man	Eu.	Dexamethasone	No change	↓(28)		87
	H-T_4			↓(34)		
Man	Eu.	Dexamethasone	No change	↓ Temp.		332
	Tox.		↓(29)	↓(50)		
Man	H-T_4	Dexamethasone	No change	↓(21)	↑(50)	68
	Tox.		↓(21)	↓(37)	↑(43)	
Man	Eu.	Dexamethasone	↓	↓		81
	H-T_4			↓		
Man	Eu.		N.S.	↓(14)	↑(85)	44,4
Man	Eu.	Dexamethasone	No change	↓	↑	327
	H-T_4		No change			
Maternal plasma	Eu.	Dexamethasone	No change	No change	No change	245
Umbilical plasma	Eu.		No change	↑(300)	↑(200)	
Man	Eu.	Betamethasone	No change	↓(66)	↑(163)	9
Man	Eu.	Betamethasone	↓(15)	↑(23)	↑(20)	113
Man	Eu.	Prednisolone	No change	↓(32)	↑(63)	113
Rat (liver)		Dexamethasone	↓	↓		160

* Numbers in parentheses refer to percentage of change after treatment, to the nearest whole number. Abbreviations used are: Eu., euthyroid; Tox., thyrotoxic; H-T_4, hypothyroid on thyroxine therapy; N.S., not significant; Temp., temporary.

dexamethasone might stimulate an increased secretion of T_4 from the fetal thyroid or, alternatively, that the rate of clearance of T_3 and rT_3 might both be reduced. There were no changes in T_4, T_3, or rT_3 in the maternal blood.

In fetal and neonatal sheep, there is a rise in plasma cortisol shortly before birth (13, 227); at the same time there is a rise in serum T_3 before and at parturition with a simultaneous fall in serum T_4 and rT_3 (101, 226, 181). Further, Nathanielsz (226) has shown that cortisol infusions in fetal lambs resulted in a fall in plasma T_4 and rT_3 and a rise in T_3; Wu et al. (342) have also found that infusions of cortisol in vivo enhanced the conversion of T_4 to T_3 in sheep fetal liver in vitro.

2. Stress. Surgical operations have been found to result in a decrease in serum T_3 and an increase in serum rT_3 in man (43, 263, 3, 54) and in the rabbit (264); this effect was thought to be due to stress, and Westgren et al. (327) have shown that i.v. infusion of ACTH into normal subjects caused a fall in serum T_3 and a rise in rT_3. However, Brandt et al. (27) showed that in patients undergoing surgery with epidural block, during which stress-induced ACTH secretion was abolished, plasma T_3 fell rapidly and there was a slight fall in plasma T_4. Askew et al. (4) attribute the fall in serum T_3 at least in part to the rise in free cortisol resulting from a fall in serum transcortin (corticosteroid-binding globulin, CBG), which could influence cellular deiodination of T_4. They tested this suggestion by assaying CBG in patients undergoing surgery with conventional anesthesia and found that serum CBG in these patients was reduced in parallel with falls in TBPA; they also found that the fall in CBG correlated with the fall in serum T_3 and rise in rT_3. They therefore suggested that serum CBG may fluctuate independently of ACTH and this may be one of the factors that controls cellular T_4 deiodination.

Finally, as might be expected, mineralocorticoids (deoxycorticosterone) have no effect on the peripheral metabolism of T_4 (327).

J. Lithium

Since its introduction as a therapeutic agent for the treatment of manic depressive disorders, lithium has been found to have a number of side effects (270) including a direct action on the thyroid, resulting in a low incidence of goiter (274, 278, 18). The major effect of lithium on the thyroid is to inhibit secretion of the thyroid hormones from the gland (47). Besides its association with goiter, lithium has been implicated with irreversible myxedema (200, 253), thyroiditis (259), thyrotoxicosis (251), exophthalmos (281), and thyroidal autoantibody production (82).

Lithium does not inhibit the peripheral conversion of T_4 to T_3 in vivo or in vitro (273, 40, 22, 186) but it does retard the T_4 clearance rate. Ohlin and Söderberg (234) found that prolonged lithium feeding to intact rats reduced the renal excretion of iodide; in thyroidectomized animals it markedly increased the half-life of ^{131}I-T_4. These findings were not, however, supported by those of Berens et al. (17), who reported that lithium feeding was without effect on T_4 turnover in rats. Spaulding et al. (297) studied the effects of lithium on T_4 turnover in six hyperthyroid and five euthyroid subjects; 50 μCi of ^{131}I-T_4 was injected i.v. and 5 days later lithium carbonate (300 mg every 8 hr) was given for a further 5 days, followed by a 5-day recovery period. The T_4 disappearance rate fell by 36% in the hyperthyroid group and by 30% in the euthyroid controls. In a similar study, Carlson et al. (48) injected ^{131}I-T_4 or ^{125}I-T_4 i.v. into five hyperthyroid and four euthyroid subjects; lithium carbonate (1.2 to 1.89 g/day) was given 9 to 10 days later but not before then. In the hyperthyroid group, the mean fall in

T_4 disappearance rate was 31%, and continued after treatment was stopped. These authors found no change in the T_4 disappearance rate in their controls. The reason for the discrepancy between the findings in the two control groups reported in these publications is not clear, but Carlson et al. have suggested that the 5-day equilibration period of labeled T_4 used by Spaulding (297) might have been too short for an accurate assessment of the T_4 disappearance rate, giving rise to an overestimate of the lithium effect.

A number of human cells, e.g. leucocytes and fibroblasts, are able to bind and deiodinate radioiodine-labeled thyroid hormones in vitro, and a T_3 receptor has been demonstrated in lymphocytes from human subjects (309). Holm et al. (157) have further shown that deiodination of labeled T_4 and T_3 by lymphocytes from hyperthyroid patients was increased 3-fold over the control value, and returned to normal after successful therapy. In lymphocytes from the hypothyroid group, T_4 deiodination was in the normal range, but fell somewhat after therapy.

Kvetny (186) studied the effect of lithium in vitro on lymphocytes from 14 euthyroid subjects and three patients with lithium-induced hypothyroidism. In two of these patients, lithium produced a slowing in ^{125}I-T_4 degradation; however, in the controls, lithium produced a rise in ^{125}I-T_4 degradation, but was without effect on ^{125}I-T_3 degradation. The stimulatory action of lithium on T_4 metabolism described here is difficult to relate to its effect on T_4 turnover in vivo. Voss et al. (324) found that in liver homogenates from lithium-treated rats, the ability to deiodinate T_4 was reduced by about one third, a result that would parallel the in vivo effect. Kvetny's unexpected finding might be due to different enzymatic processes occurring in liver cells and in lymphocytes.

K. Radiographic Contrast Media

Iodine-containing contrast media* have been known for a long time to interfere with thyroid function tests, partly owing to the liberation of iodine (as iodide), which invalidates thyroidal radioiodine uptake tests, and partly because of their high iodine contents, which invalidate PBI estimations (261). These compounds have a very variable rate of metabolism, ranging from a few days (diatrizoate, Hypaque, amidotrizoic acid) to many years (iophenoxic acid, teridax) (261, 77). Sodium ipodate (Oragrafin, Biloptin Na) interferes with the T_3 red cell uptake test (73) and with the T_3 resin and resin sponge tests (29, 31, 210).

There have been a number of reports of episodes of hyperthyroidism after the administration of radiographic contrast media, presumably due to the rapid liberation of iodide, causing jodbasedow (24, 182, 180, 311). Many of these reports did not specify the contrast agent used (231, 24, 25, 25a, 284, 144). Fairhurst and Naqvi (94) described a patient with hyperthyroidism after ipodate administration; Steidle et al. (298) showed that in 119 patients from a German endemic goiter area who received contrast agents, 18 were found to be hyperthyroid after 28 days. The highest incidence (27.9%) occurred after oral cholecystography with calcium ipodate and the lowest (5.3%) after urography with diatrizoate. Cholecystography with ioglycamic acid (Bilvistan, Biligram) resulted in an incidence of hyperthyroidism of 15.8%. However, there is one report of neonatal hypothyroidism after amniocentesis involving contrast agents (268).

Mahlstedt and Joseph (210) were the first to demonstrate a rise in serum T_4 after the administration of a single dose of 3 g of iodobenzamic acid (Osbil) to patients with autonomous thyroid adenomas; the serum T_4 remained elevated for 3 months after the dose. Turner et al. (310) also reported raised serum T_4 and T_3 after i.v. pyelography. Bürgi et al. (39) showed a rise in serum T_4 after cholecystography with Na iopanoate (Colepax, Telepaque, Bilijodon-Na) in both normal and euthyroid goitrous patients, with a concomitant fall in serum T_3 and rise (50%) in serum rT_3. In a group of myxedematous patients receiving T_4 replacement therapy (0.1 to 0.2 mg/day) iopanoate caused a fall in serum T_3 and a rise in serum rT_3. Intravenous urography with diatrizoic acid and cholangiography with ioglycamic acid did not significantly affect the peripheral metabolism of T_4.

Wu et al. (340) showed that a single dose of 3 g of ipodate in normal subjects, in four hyperthyroid patients, and three hypothyroid patients receiving T_4 therapy caused a pronounced fall in serum T_3 and a rise in serum rT_3. The same group (341) then studied the effect of repeated doses of ipodate given at five 3-day intervals in hyperthyroid patients and found that both serum T_4 and T_3 fell while serum rT_3 rose rapidly and fell rapidly after each dose. Chopra (64) concluded that ipodate affects only outer ring deiodination of T_4, thus inhibiting the formation of T_3 and the degradation of rT_3. The same conclusion was reached by Beng et al. (16), who studied the effect of ipodate on patterns of T_4, T_3, and rT_3 in normal subjects and found a marked inhibition of T_3 formation as well as an inhibition of breakdown of rT_3. Suzuki et al. (302) observed falls in serum T_3 and rises in serum rT_3 in euthyroid subjects after treatment with ipodate, iopanoate, iobenzamic acid, and tyropanoic acid (Bilopaque, Lumopaque). In all cases there was a slight rise in serum T_4, the greatest change occurring after ipodate. Obregon et al. (233, 233a) observed inhibition of

* The chemical names and iodine contents of contrast media described are: (a) diatrizoate Na,3,5-bis(acetylamino)-2,4,6-triiodobenzoic acid Na, I, 59.87%; (b) iobenzamic acid, N-(3-amino,2,4,6-triiodobenzoyl)-N-phenyl-β-alanine, I, 57.51%; ioglycamic acid, 3,3-[oxybis-((1-oxo-2,1-ethanediyl)imino)]bis-2,4-6-triiodobenzoic acid I, 40.93%; (c) iopanoic acid, 3-amino-α-ethyl-2,4-6-triiodobenzene-propanoic acid, I, 66.69%; (d) iophenoxic acid, α-ethyl-3-hydroxy-2,4,6-triiodobenzene-propanoic acid, I, 66.57%; (e) iothalamic acid, 3-(acetylamino)2,4,6-triiodo-5-[(methylamino)carbonyl]benzoic acid, I, 62.01%; (e) ipodate, 3-[(dimethylaminomethylene)-amino]-2,4,6-triiodocinnamic acid, I, 63.67%; (f) tyropanoic acid, 3-butyramido-α-ethyl-2,4,6-triiodohydrocinnamic acid, I, 57.42%.

deiodination of labeled T_4 to T_3 in rats pretreated with iopanoic acid.

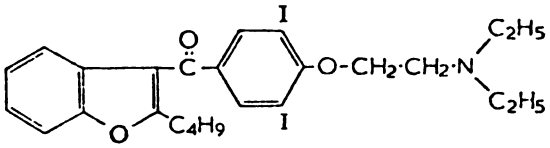
The effects of contrast media on TSH are not always consistent. Wu et al. (340) found no change in TSH levels after ipodate treatment, whereas Bürgi et al. (39), Suzuki et al. (302), and Beng et al. (16) all found rises in TSH after administration of contrast media. Suzuki (302) considers that the rise in serum TSH is secondary to the fall in serum T_3 produced by these compounds. Kleinmann et al. (181a) have confirmed the rise in TSH after administration of iopanoate.

The effect of contrast media on hepatic binding of T_4 has been studied by Felicetta et al. (100). They administered ^{125}I-T_4 to normal subjects whose thyroids were blocked with iodide and counted the radioactivity over the liver and in the serum. Oral tyropanoate produced a rapid decrease in ^{125}I counts over the liver, the lowest level being reached 4 hr after the dose; thereafter the liver counts slowly returned to the pretreatment level after 20 to 30 hr. In patients with viral or alcoholic hepatitis, in whom the liver has a reduced T_4-binding capacity (52), the effect of tyropanoate on T_4 binding was quite small. Oral ipodate was also shown to discharge T_4 from the liver. Felicetta et al. (100) point out that the only other treatment that causes the rapid discharge of T_4 from the liver is diethylether anesthesia, and that such a discharge may be the cause of T_4 redistribution during halothane anesthesia (106, 249, 250).

The conversion of ^{131}I-T_4 to ^{131}I-T_3 in rabbit anterior pituitary tissue was first demonstrated by Ford and Gross (105a); this has been considered recently (287, 288) as a means whereby the release of TSH is locally controlled. Pituitary T_4-5′-monodeiodination is inhibited in rats by in vivo administration of iopanoic acid (233) and by incubation of the drug in vitro with rat liver and kidney homogenates (64, 66, 175), by rat anterior pituitary homogenates (173), and by rat cerebral cortex and cerebellum (72). Unlike the liver enzyme, the pituitary deiodinase is unaffected by PTU (56). It has been shown that the liver and pituitary deiodinases differ in other respects: The liver enzyme has decreased activity in thyroidectomized rats and in starved animals; its activity is increased in T_4-treated rats (176). The pituitary enzyme is unaffected by fasting, is inhibited by T_4 administration and has increased activity in hypothyroid animals. Yet another difference is shown during maturation in rats (57): The liver enzyme either increases somewhat between the ages of 2 and 21 days or is unchanged over this period (when DTT is added to the incubation medium). The pituitary enzyme has 3.5 times the activity in 2-day-old animals as it has in 28-day-old animals, after which it remains constant to maturity (72 days).

L. Amiodarone

The antianginal, antiarrhythmic drug amiodarone, 2-butyl-3(4,diethylaminoethoxy-3,5-diiodobenzoyl) benzofuran, contains 39.4% I and has been thought to have structural resemblance to T_4. It has no thyromimetic activity, nor does it cause iodine-induced hypothyroidism as does the chemically related drug benziodarone (138), although it might do so in subjects with underlying thyroid disease such as Hashimoto's thyroiditis.



Broekhuysen et al. (35) studied the metabolism of amiodarone in a number of laboratory animals and in man. In the latter, a dose of 300 mg/day produced a positive iodine balance during the first month of treatment after which equilibrium was reached with a daily excretion of 9 mg of iodide. The half-life of the drug was between 28 and 100 days. The drug inhibited thyroidal radioiodine uptake and invalidated PBI measurements and these effects lasted for several months after treatment was stopped; however, there were no symptoms of hypothyroidism or thyroid dysfunction. Nevertheless, a few cases of hypothyroidism and of hyperthyroidism have been reported in patients maintained on amiodarone, but such complications are rare (179).

Singh and Vaughn Williams (290) studied the effect of amiodarone on cardiac muscle in rabbits treated with 20 mg/kg for up to 6 weeks. No effect on the resting potential or action potential height of isolated atrial or ventricular fibers was seen, but the drug greatly prolonged the duration of the action potentials. This effect was completely abolished by a daily injection of 5 μg of T_4 (a dose that would not entirely suppress endogenous T_4 secretion in the rabbit); prolonged administration of the drug had no effect on thyroid weight but was associated with a reduction in body weight. KI administered with amiodarone in a dose equivalent to the iodine content of the drug did not reverse its action on cardiac action potentials, and was without effect on body weight. The authors suggested that the effects of the drug resembled those of thyroidectomy.

Later the same group (260) evaluated thyroid function in 12 patients with ischemic heart disease treated with 200 mg of amiodarone three times a day for up to 6 weeks; they found that serum T_3 levels tended to fall, and those of T_4 to rise, but not outside the normal range. The effects of the drug were still present 4 weeks after cessation of treatment, indicating a rather slow removal from body depots. Thyroid function was not depressed. Burger et al. (37) examined the effects of amiodarone on T_4 metabolism in euthyroid males treated as follows: (a) amiodarone alone, 400 mg daily for 28 days; (b) amiodarone, 400 mg plus T_4, 300 μg daily for 6 days; (c) T_4 alone, 300 μg daily for 16 days, and Lugol's solution (150 mg of I daily) for 28 days. Amiodarone alone or with T_4 produced a rise in T_4, a fall in T_3, and a very marked rise (about 200%) in rT_3. That the effect of amiodarone was

not principally due to iodide produced by metabolism of the drug was shown in the experiment with Lugol's solution, in which a temporary fall in serum T_4 and T_3 levels was followed by a slow return to normal levels (37). Iodide administration has been shown to block the secretion of hormonal iodine from the thyroid (312); however, from these experiments and those described above, it would appear that iodide has only a minor role in the effect of amiodarone on thyroidal iodine metabolism. Its chief effect is an inhibition of the formation of T_3 from T_4 and probably a decreased degradation of rT_3. Amiodarone had no effect on the radioimmunoassays of T_4, T_3, or rT_3. These findings have been confirmed by Melmed et al. (215a).

M. Iodide

While iodide has long been known to influence the secretion of thyroid hormones from the gland, it has not been thought to influence thyroid hormone metabolism. In 1966, DeGroot (80) investigated the effect of iodide in three hyperthyroid patients maintained on sufficient methimazole to inhibit endogenous T_4 production. These were then given a dose of ^{131}I-T_4 i.v.; when the slope of labeled T_4 disappearance was established, the patients received 10 mg of KI orally every 8 hr. This treatment was without effect on the slope of T_4 disappearance.

Galton and Ingbar (111) also found that, in rats, iodide in huge doses (5 g of KI/rat/day) was without effect on either the deiodinative or gastrointestinal pathways of ^{131}I-T_4 metabolism. Recently, however, this subject has been reexamined by Grubeck-Loebenstein and Klieber (131); they treated healthy volunteers with brine containing 25 mg of iodide per day for 3 weeks and found that the concentration of serum T_3 fell by 11% while that of T_4 and rT_3 rose by 8% and 19%, respectively. It would be interesting to know whether such an effect of iodide could be seen in hyperthyroid patients.

From the work of Galton and Ingbar (111) it would appear that the rat is insensitive to iodide and hence is not always a suitable experimental animal for comparison with humans. In this respect it may also be noted that Galton (110), in her study of the fractional rate of T_4 degradation, found the rat insensitive to exogenous T_4.

IV. Concluding Remarks

Among the varied types of drugs, toxins, and hormones that influence the transport, distribution, and metabolism of thyroid hormones, few if any lead to permanent, irreversible alterations in thyroid function. Furthermore, except for those agents such as PTU or lithium that also inhibit thyroid hormone synthesis or secretion, few of the drugs we have considered lead to significant changes in metabolic status. This generalization is a tribute to the ability of the body to maintain a normal hormonal economy.

One source of confusion that has prevented a more complete understanding of the action of drugs on thyroid hormone transport and metabolism in humans has been the tendency to extrapolate to man from data obtained in animal species that do not have TBG (e.g. rodents). To the extent that a given drug, hormone, or toxin affects plasma binding of thyroid hormone, information derived solely from studies in animals lacking TBG could be misleading. The solution, of course, is to obtain data in humans or in other primates.

A second cause of confusion is the tendency of many drugs to exert multiple effects or to act at many levels of thyroid hormone economy. This is especially true in the case of agents with structural resemblance to the thyroid hormones. Such agents often compete with the hormones for binding to plasma proteins and also act at the tissue level by displacing hormone from cellular binding sites and/or enzymes that metabolize the hormones. The in vivo effects of this type of drug are much more complex than those of an agent that has one action, e.g. to raise or lower the plasma concentration of TBG.

In spite of these complications, studies of the effects of drugs have often led to important advances in our knowledge of thyroid hormone transport and metabolism.

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