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Thyroxine turnover : review of literature and consideration of preliminary studies in patients with malignant disease

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THYROXINE TURNOVER: REVIEW OF LITERATURE AND CONSIDERATION OF PRELIMINARY STUDIES IN PATIENTS WITH MALIGNANT DISEASE

by

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Preface

Physicians have shown a long interest in the thyroid gland with a documented history dating back to the time of Ebers Papyrus (1500 B. C.). Since the introduction of radioactive iodine (^{131}I) tracer materials in 1945, scientists have been able to explore the rates of metabolism, turnover, and fate of the thyroid hormones in various clinical situations. The objective of this study is to review the literature concerning the effects of various factors on thyroid hormone metabolism and disposition as measured by rates of disposal of radioactive iodinated thyroid hormones.

Background: Thyroid Hormone Synthesis

Concentration Mechanism, Uptake.--

Thyroid hormone is synthesized in the thyroid gland utilizing as raw materials; iodine obtained from the food and water ingested, and tyrosine, one of the synthesized amino acids. The ingested iodine is reduced to iodide before absorption from the gastrointestinal tract and appears in the blood as inorganic iodide (I^-). The iodide circulating in the blood is actively concentrated in the

epithelial cells of the thyroid gland, which have a greater avidity of iodide than other cells of the body. Small amounts of iodide are concentrated in saliva, sweat, gastric secretions, and the mammary gland as well.[1,2,3] The activity of the transport mechanism concentrating the iodide is regulated and increased directly by thyrotropin, the thyroid stimulating hormone (TSH) of the anterior pituitary gland, and indirectly via intrinsic systems within the thyroid gland regulated by iodine stores.[4]

Binding.--

The inorganic iodine that accumulates in the follicular epithelium of the thyroid gland is oxidized to a higher valence form, possibly iodine (I_2) or hypoiodite (I^+) through a reaction mediated by an intrathyroidal peroxidase enzyme.[3] This highly reactive form of iodine exists only momentarily as it combines rapidly with tyrosine groups in thyroid proteins to form mono-iodotyrosine (MIT), which is further iodinated to di-iodotyrosine (DIT).[2]

Coupling.--

The two iodotyrosines then undergo oxidative coupling, possibly again mediated by the thyroidal peroxidase to yield a variety of iodothyronines, including 3,5,3'-triiodothyronine (T_3) and 3,5,3',5'-tetra-iodothyronine, hereafter referred to as thyroxine (T_4). It is postulated

that thyroxine is formed by the coupling of two molecules of di-iodotyrosine. 3,5,3'-tri-iodothyronine may be produced either by the coupling of one molecule each of MIT and DIT, or the loss of one iodine atom from the thyroxine molecule.[3]

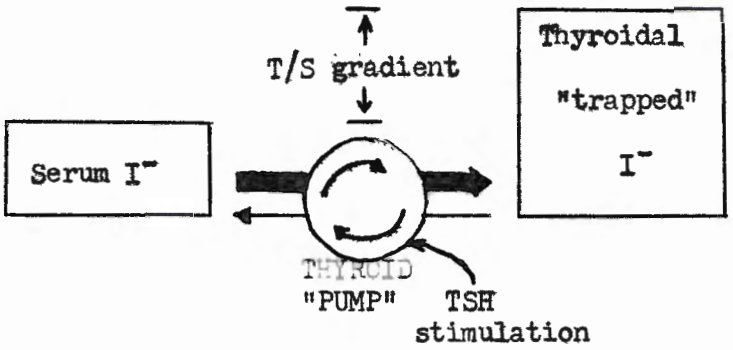
Release.--

The iodothyronines, T_3 and T_4 as well as the iodinated amino acids, MIT and DIT are stored in the thyroid follicle as residues of thyroglobulin. The thyroid hormones are released into the blood stream under the stimulus of the thyrotropic hormone.[1,3] This hormone, by means of thyroidal proteases, hydrolyzes the storage protein, thyroglobulin to release MIT, DIT, T_3, and T_4. The T_3 and T_4 released are transported across the acinar wall of the thyroid gland into the blood stream. The MIT and DIT are prevented from entering the circulation by action of an iodotyrosine deiodinase which removes the iodide. This iodide is in part reutilized for synthesis of hormone and part is lost from the gland into the circulation.[2,3]

Transport.--

In the blood stream thyroxine is almost entirely bound and T_3 partially bound to the plasma proteins. Electrophoretic analysis of the thyroid binding proteins indicate that thyroxine is bound primarily to an interalpha-globulin termed thyroxine-binding globulin (TBG) and to a pre-albumin, thyroxine-binding pre-albumin (TBPA). Thyroxine

I. TRAPPING



II. BINDING

I^- —oxidation→ $[I^o]$ + thyroglobulin → monoiodotyrosine (MIT)
diiodotyrosine (DIT)

inhibition

III. COUPLING

2DIT ⟶ thyroxine (T_4)
1 MIT + 1DIT ⟶ triiodothyronine (T_3)

thyroglobulin

IV. RELEASING

T_4 - T_3-MIT-DIT-thyroglobulin —enzymatic hydrolysis; thyrotropin activated→ T_4 + T_3 + MIT + DIT

MIT + DIT (thyroid) —tyrosine; deiodinase→ tyrosine + I^- (recycled)

Fig. 1 Sequential stages of intrathyroidal synthesis and secretion of thyroid hormones.

is also bound secondarily to albumin and perhaps to a Beta globulin. The interaction between thyroxine and its binding protein conforms to a reversible binding equilibrium in which the majority of the hormone is bound and only a very small proportion is unbound or free. T_3 is not bound by TBPA and is bound by TBG only weakly, leaving a large proportion of T_3 unbound. Only the free form of either hormone is thought to be available to the tissues, thus the metabolic rate as well as rate of metabolism of the hormone correlates more closely with the concentration of free hormone than with the total concentration of hormone. The weakly bound T_3 is thus removed from the circulation more rapidly than the more tightly bound thyroxine. However, the greater metabolic activity of T_3 permits lower concentrations of hormone to alter metabolism as compared to the more tightly bound thyroxine. The binding capacity of the thyroid binding proteins may change the relative amounts of free to bound hormone. The binding activity of TBG is increased in some states such as estrogen therapy and decreased in patients treated with the so-called "anabolic" steroids. TBPA binding activity is not known to be increased in any disorder, but is frequently decreased in a variety of conditions.[4,5]

Effects of Thyroid Hormones.--

The effects of the circulating hormones are predom-

inately two: 1) participation in the "feedback" regulation system which maintains the concentration of thyroid hormone in the blood, and 2) alteration of metabolism by its action on the peripheral tissues.[3]

Regulation of Thyroid-Pituitary Axis.--

Thy hormonal synthesizing activity of the thyroid gland is controlled predominately by TSH. Release of TSH from the anterior pituitary is regulated, at least in part, by TSH releasing factor from hypothalamic centers and generally depends upon the quantity of thyroid hormones available to these tissues. A reduction in the effective concentration of circulating thyroid hormone stimulates TSH output, which in turn, leads to an increase in secretion and size of the thyroid gland. Conversely, an excess of circulating effective thyroid hormone tends to depress secretion of TSH and so, in turn, to reduce thyroid activity and size. From the above brief description it is shown that there is a direct feedback relationship between the hypophysis and the thyroid.[1,2,3] However, the subtile modulation of function of the gland demanded by complex life situations requires the participation of the central nervous system.[6]

Regulation of Metabolism.--

The physiological effects of thyroid hormone are many and varied, so much so, that there has been no agreement

as to what may be considered the "primary" action, if there is one. In an attempt to classify the disorders based on effective concentration of circulating hormone, the terms hypothyroid, euthyroid, and hyperthyroid are used. Hypothyroid refers to the absolute or relative insufficient supply of thyroid hormone necessary to maintain the organism in a normal, or so-called "euthyroid" state. The hyperthyroid state is considered to be a relative or absolute excess of circulating hormone above that necessary to maintain in that particular organism a euthyroid state. The effects of circulating hormone have been studied largely by observing the intact organism, its tissues or organs as they fit into one of the above classes, and how their development, growth, metabolism, and function are altered by varying levels of thyroid hormones in the experiments shown or in the system studied.[7,8,9]

Effect on Enzymatic Processes.--

Thyroid hormone, like other hormones, may act by controlling the rates of metabolic enzymatic processes. In some cases the direct effects of T_4 at the reacting site is required, whereas in others the hormone exerts an indirect effect by altering the concentration of one of the components of the system. Studies[10] of regulation of metabolism have focused on the control of: 1) respiration or energy production, 2) the levels of substrate or enzyme, 3) synthetic

rates of these materials, and 4) the spatial and structural relations between these materials. At least thirty-three enzyme systems[10] are enhanced or inhibited by thyroid hormones, some of the more important of these systems being: 1) Metal binding. Some enzyme systems such as urease and ascorbic acid oxidase are stimulated by the removal by T_4 of inhibitory metals including cupric ion and magnesium.[10] 2) Oxidation as well as oxygen consumption is markedly stimulated by thyroid hormones.[10] Since 1895 the thyroid hormones have been known to have a remarkable effect on the metabolic rate. It has been established that skeletal muscle, heart, diaphram, liver, kidney, salivary gland, gastric mucosa, and skin have metabolic rates and oxygen consumption roughly proportional to the level of circulating thyroid hormones. The most striking effect of T_4 is the stimulation of oxygen consumption, and many attempts have been made to explain the mechanism. There is, however, no compelling reason to believe that stimulation of oxygen consumption or energy production is the single fundamental action of the hormone.[11] Thyroid hormone is observed to increase the oxidative activity that is seen in mitochondrial glycerophosphate dehydrogenase and electron transport where components - cytochrome c and cytochrome oxidase are materially increased with increasing levels of circulating thyroid hormones. 3) Oxidative phosphorylation

is markedly increased by T_4 uncoupling of phosphorylation from oxidation as well as direct stimulation of oxidative phosphorylation by T_4.[10]

These enzyme alterations are manifest on a larger scale by the alteration in carbohydrate, fat, and protein metabolism. Carbohydrate metabolism is altered in two ways. There is an increase in the rate of glucose adsorption and an increase in the rate of cellular utilization of glucose.[7] Fat metabolism is also altered as a result of increased carbohydrate metabolism with increased thyroid hormone concentration. The more rapid consumption of carbohydrate is followed by increased utilization of fat for energy. With decreased thyroid hormone less carbohydrate is used, and fat deposition occurs with the increase in weight very frequently seen in hypothyroid states.[9] Protein anabolism and catabolism are stimulated by thyroid hormone. Negative nitrogen balance and excessive protein catabolism with tissue wasting may ensue with excess hormone.[8]

Normal growth and development appear to depend in part upon direct action of thyroid hormone, but also in part upon the action of other hormones, particularly growth hormone, acting in concert with thyroid hormone.[7] The parameter most often effected in growth is that of

protein metabolism.[6,7,8]

Effect on Weight.--

Greatly increased levels of effective thyroid hormone concentration almost always decreses body weight and, conversely, greatly decreased levels of thyroid hormone almost always increases body weight. These effects, however, do not always occur with moderate changes in thyroid hormone production.[7,8]

Effect on Cardiac System.--

The change in metabolism induced by thyroid hormones causes an alteration in the demand of the tissues for nutrients. The cardiac output tends to be roughly proportional to the metabolic rate, being low in hypothyroidism and high in hyperthyroidism. In the presence of excessive thyroid hormone concentrations the cardiac output may rise up to fifty per cent or more above normal.[8] The heart rate increases considerably more under the influence of thyroid hormones than would be expected simply due to the increases in cardiac output. It is suggested that thyroid probably has a direct effect on excitability of the heart.[11] The blood volume is observed to increase slightly with thyroid hormone excess and decrease with deficient hormone. These changes are at least partly caused by vasodilatation and vasoconstriction respectfully with resulting compensatory changes in blood

volume.[12] The increased rate of run-off of blood through the peripheral vessels with increased levels of hormone causes the pulse pressure to be increased with the systolic pressure elevated 10-20 mm Hg and the diastolic slightly reduced. The opposite effects with a hypotensive patient are seen with decreased levels of thyroid hormones.[7,9] Mild increases in thyroxine levels are often associated with vigorous, brisk, and rapid contractions. In contrast, with a marked increase in thyroid hormone the heart muscle strength becomes depressed because of excessive catabolism. In hypothyroidism there is a weak sluggish heart beat with low voltage deflection on the electrocardiogram.[9,11]

Effect on Respiration.--

The altered rate of metabolism with elevated or depressed levels of hormone cause changes in utilization of oxygen and formation of carbon dioxide. In hyperthyroidism, an increased production of carbon dioxide and decreased oxygen concentration activate all the mechanisms that increase rate and depth of respiration. The opposite effects are seen in hypothyroidism.[7,8,9]

Effect on the Gastrointestinal Tract.--

In addition to the increased rate of absorption of foodstuffs, thyroxine increases the rate of secretion of the digestive juice and the motility of the GI tract.

Effect on the Nervous System.--

In general, thyroid hormone increases the synaptic activity but does not influence peripheral nerve activity.[7,11]

Metabolism of Thyroid Hormones.--

The metabolic disposition of thyroid hormones is being studied extensively. Earlier studies (to be discussed later) demonstrate accelerated rates of thyroxine disappearance from the serum in hyperthyroidism and diminished rates in hypothyroidism. The significance of this became clear with the demonstration of return to normal rates of disposition with correction of either hypothyroidism or hyperthyroidism.

It therefore became evident that rates of thyroxine utilization might reflect intrinsic rates of metabolic activities, as these may or may not be induced by action of thyroid hormone.

The study of metabolic disposition of thyroid hormone has led to significant advances in determining various factors which lead to accelerated rates of thyroxine disappearance. Decreased binding capacity of thyroid binding proteins allows for more free thyroxine as is manifested by increased utilization and metabolic activity.[4] Hepatic function alterations are shown by decreased binding of hormone by the liver and subsequent rapid loss from the body via the biliary and gastrointestinal tracts.[12] The

three major routes available for thyroid hormone metabolism are: 1) Phenolic conjugation. Administration of thyroxine and T_3 have been observed to be followed by a rapid appearance of increased amounts of Beta-glucuronides of these molecules in the liver. These appear next in the biliary tree and subsequently in the gastrointestinal tract where the conjugates then undergo intestinal hydrolysis. The free hormone or derivative is then either reabsorbed or excreted in the feces.[10] 2) Oxidative deamination and transamination. The alanine side-chain of the T_3 and T_4 undergoes oxidative deamination and transamination to the acetic derivative in the kidney. These iodothyroacetic acids then further undergo phenolyic conjugation and deiodination like their parent amino acids.[10] 3) Deiodination. This pathway involving removal of the iodine atom, is the most important route of thyroid hormone met bolism. This is mediated by a number of enzymes in the body which can attack only the free or non-protein bound substrate.[10,13]

All three of the above pathways operate in the liver with conjugation being the most prominent. Deamination is the most pronounced in the kidney, whereas deiodination is the only metabolic pathway in skeletal muscle.[11,12,13,14,15]

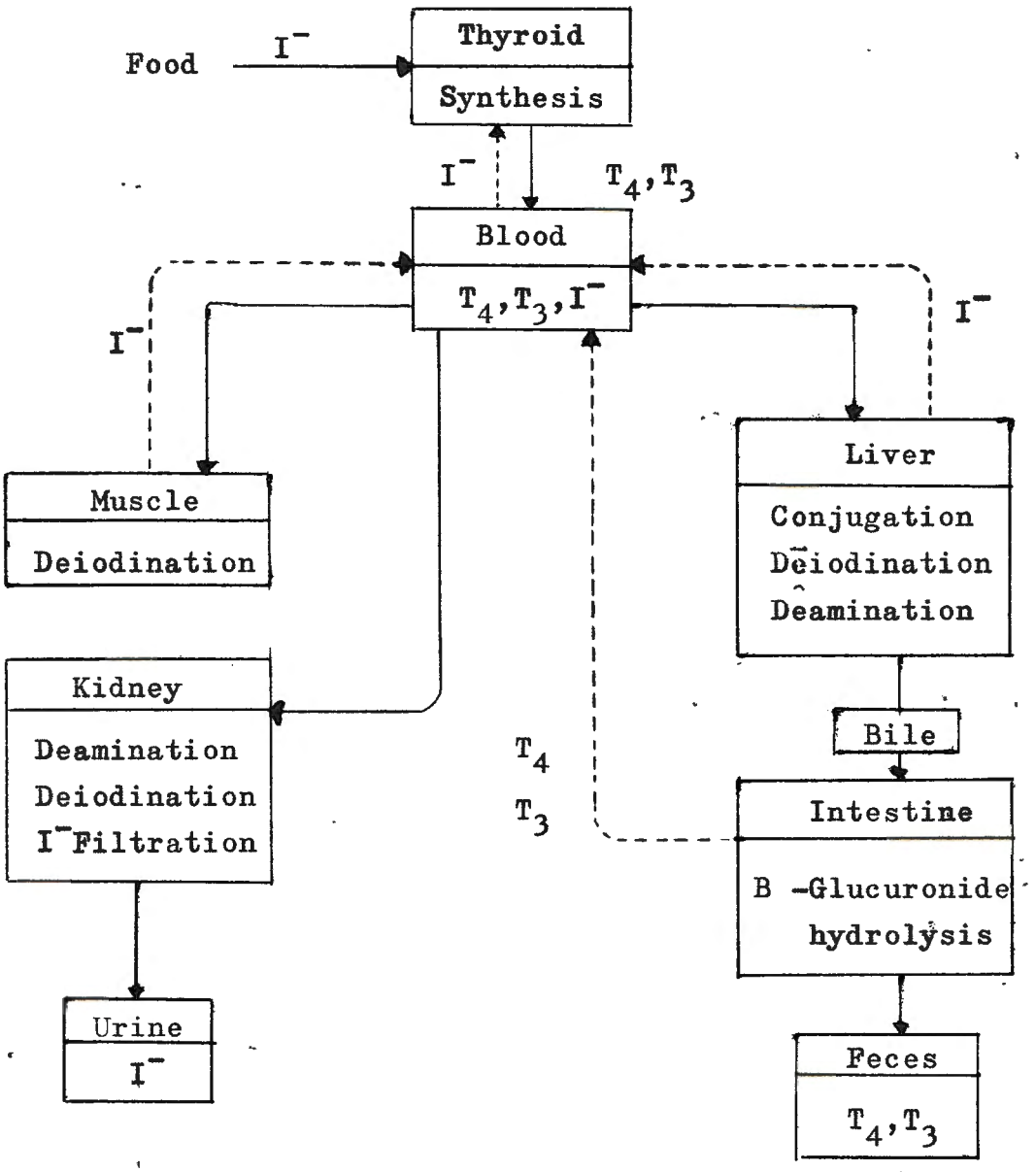
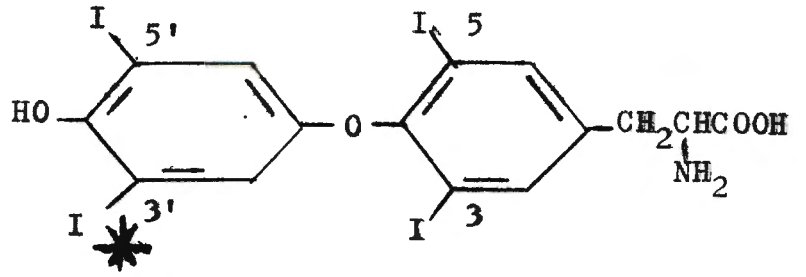


Figure 2. Scheme for the major pathways of distribution and metabolism of thyroxine and tri-iodothyronine at the whole body level.[6]

Thyroxine Turnover and Metabolism Analysis

Thyroxine turnover and metabolism is studied by the use of ^{127}I and ^{131}I-thyroxine which is a chemically synthesized L(-)thyroxine which has been tagged with radioactive iodine in the 3'-position.[16]



^{131}I-3,5,3',5'-tetra-iodothyronine

^{131}I-L(-)thyroxine

Tracer Materials.--

Tracer materials such as ^{131}I-thyroxine fulfill three important requirements: 1) They are as a rule biologically indistinguishable from the substance under investigation and therefore may be assumed to undergo the same metabolic changes. 2) They are administered in small amounts which do

not disturb the dynamic equilibrium of the system as a whole. 3) Since the tracers are not in a steady state when introduced instantaneously into one portion of the system, they exhibit quantitative changes which may be mathematically analyzed and described as a function of time, thus reflecting the various rates of reactions and transfers with the physiological (non-tracer) metabolite under investigation.[17]

The tracer is administered intravenously (IV) as a sterile solution in amounts varying from less than 1 microcurie to over 100 microcuries.[18,19,20,21,22,23,24,25,26,27] The tracer equivalent is 20 millicuries per milligram of thyroxine.[19]

Collection.--

Following the IV administration, the ^{131}I-T_4 distributes throughout the space of distribution of T_4 and mixes with the endogenous thyroxine. Sampling of blood as serum or plasma is then made at various time intervals dependent on the parameter of thyroxine distribution or disposition dynamics desired to be investigated.[18,19,20]

Data Analyzation.--

The data obtained is usually analyzed as a semi-logarithmic curve. A typical semilogarithmetic plot is expressed in fig. 3.

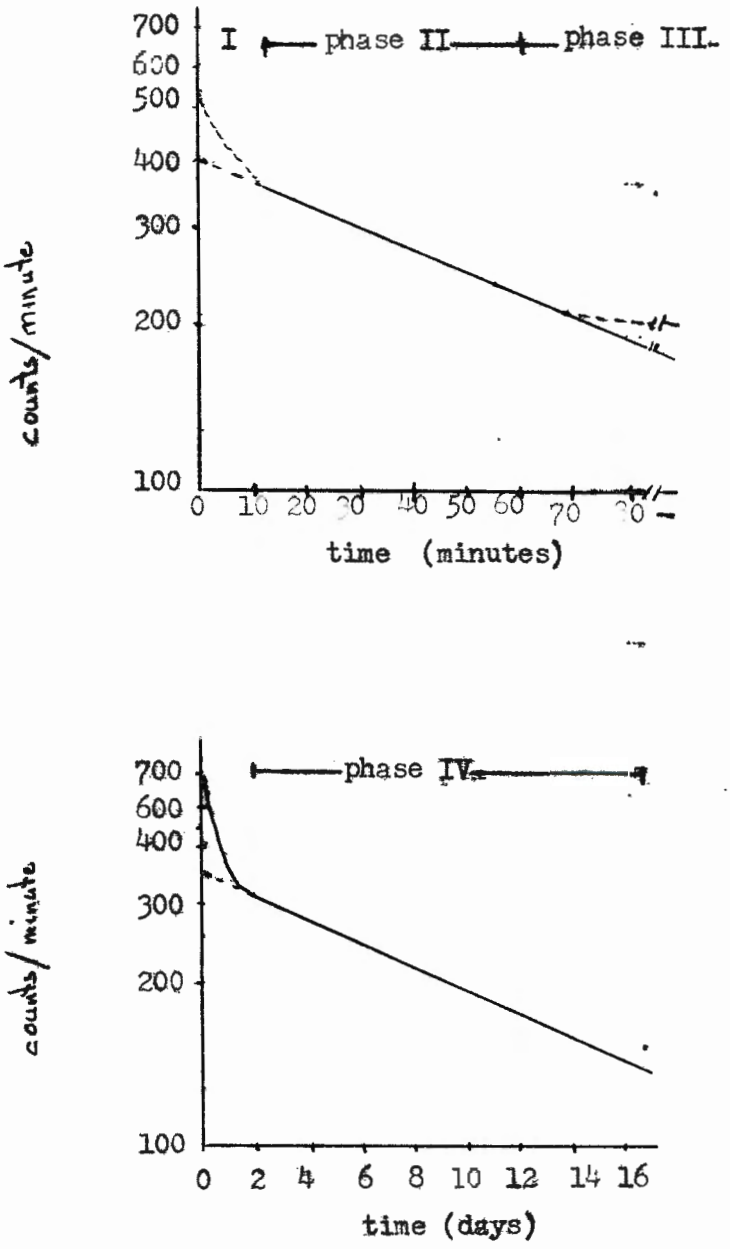


Figure 3. Semilogarithmic plots of selected studies to illustrate the kinetics of radiothyroxine disappearance curves. Plot at top of page shows early changes and figure below shows later changes.

Graphic Components of ^{131}I-T_4 Metabolism.--

Initially when the ^{131}I-T_4 is injected intravenously there is a rapid disappearance of the radioisotope from the blood. This first component which extends from 0 to 20 minutes represents mixing and dilution of T_4 in the blood. The second phase extends from approximately 15 to 60 minutes and is believed to reflect primarily the distribution rate of labelled thyroid hormone throughout the extrathyroidal thyroxine pool with intravascular-extravascular competition for the T_4 and trapping of T_4 by certain organs, particularly the liver. The third phase is curvilinear and extends for a period of several days. It represents mixing of T_4 throughout the body with the establishment of equilibrium between labeled and unlabeled thyroxine. The final phase is linear and represents utilization after equilibrium between the labelled and unlabeled thyroxine. Thus this final phase represents thyroxine utilization.[18,20,21,23,24,25,28,29,30,31]

Considerable work has been done on the kinetics of iodine metabolism to ascertain the "thyroxine space". This is accomplished by considering metabolic systems consisting of three distinct interchanging pools(Q_1, Q_2, Q_3), i.e., three distinct aggregates of the metabolite which differ from each other either by virtue of anatomical location or physio-chemical states. The initial pools

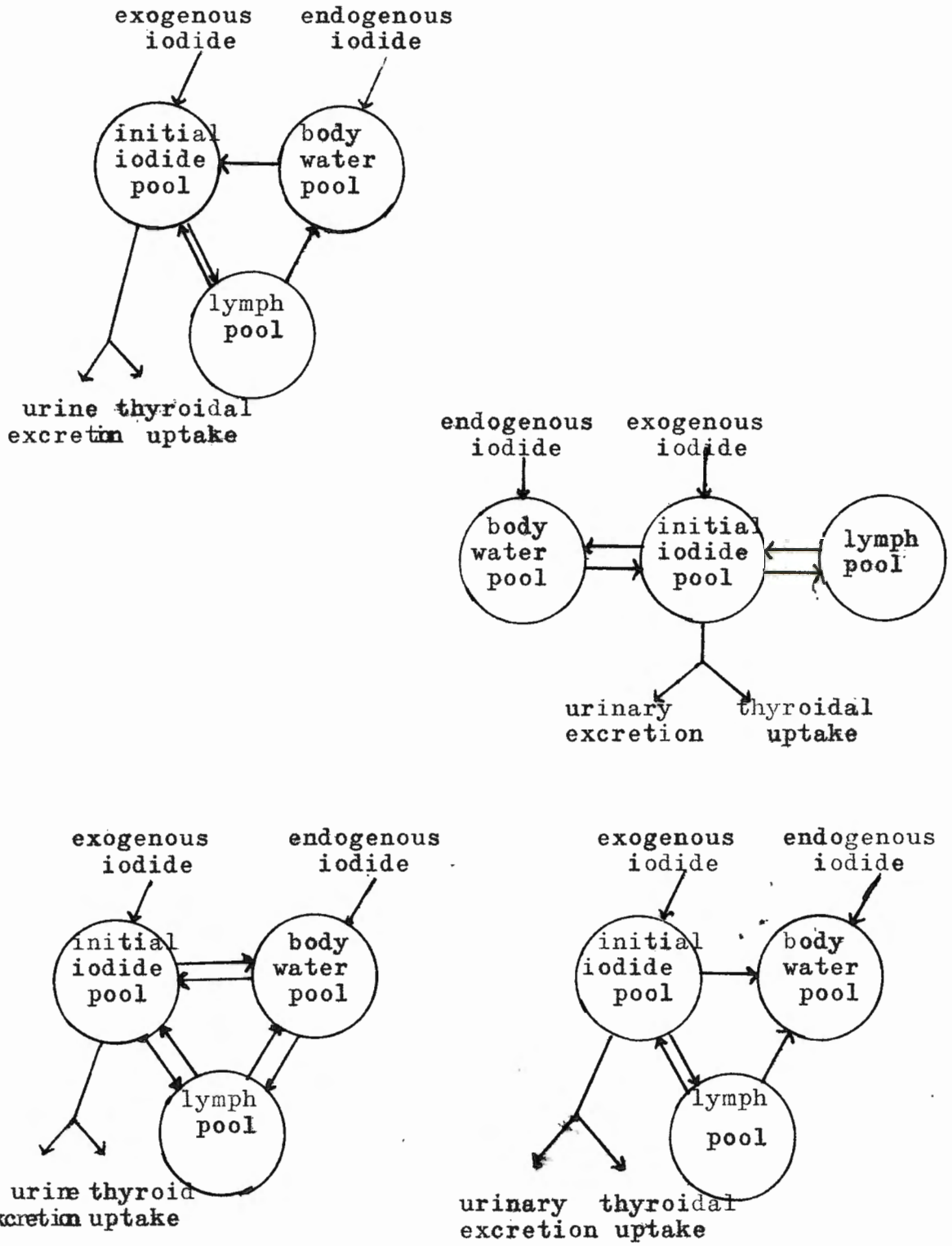


Fig. 4. Schematic Representation of Kinetics of Iodine Metabolism Immediately Following Injection of Tracer Material.[33]

which describe the forces and sites of distribution of the labelled thyroxine immediately after injection are:

Q_1) Initial miscible iodide pool consisting primarily of iodide in plasma, red cells, gastric mucosa, salivary glands, and thyroid gland.

Q_2) Iodide in "central lymph" and possibly in peripheral lymphatics.

Q_3) Iodide in "remaining" body water.[32,33]

These pools are best described by referring to Fig. 4, taken from Sharney[33], which shows five schematic representations of the possible kinetics following injection of the labelled thyroxine.

The final phase (Fig. 5), pertaining to the kinetics of the metabolism of the tracer element following equilibrium with the endogenous thyroxine as found in the body at the time of injection, has been extensively studied. Again the three pool system (Q_1, Q_2, Q_3) is used to describe the interaction and forces active in the kinetics of metabolism. The three pools are:

Q_1) Plasma pool consisting of iodine in plasma thyroxine.

Q_2) "Intrahepatic" pool consisting of iodine in intrahepatic thyroxine.

Q_3) Lymph pool consisting of iodine in thyroxine of lymph, other interstitial fluids, and remaining water.[34,35]

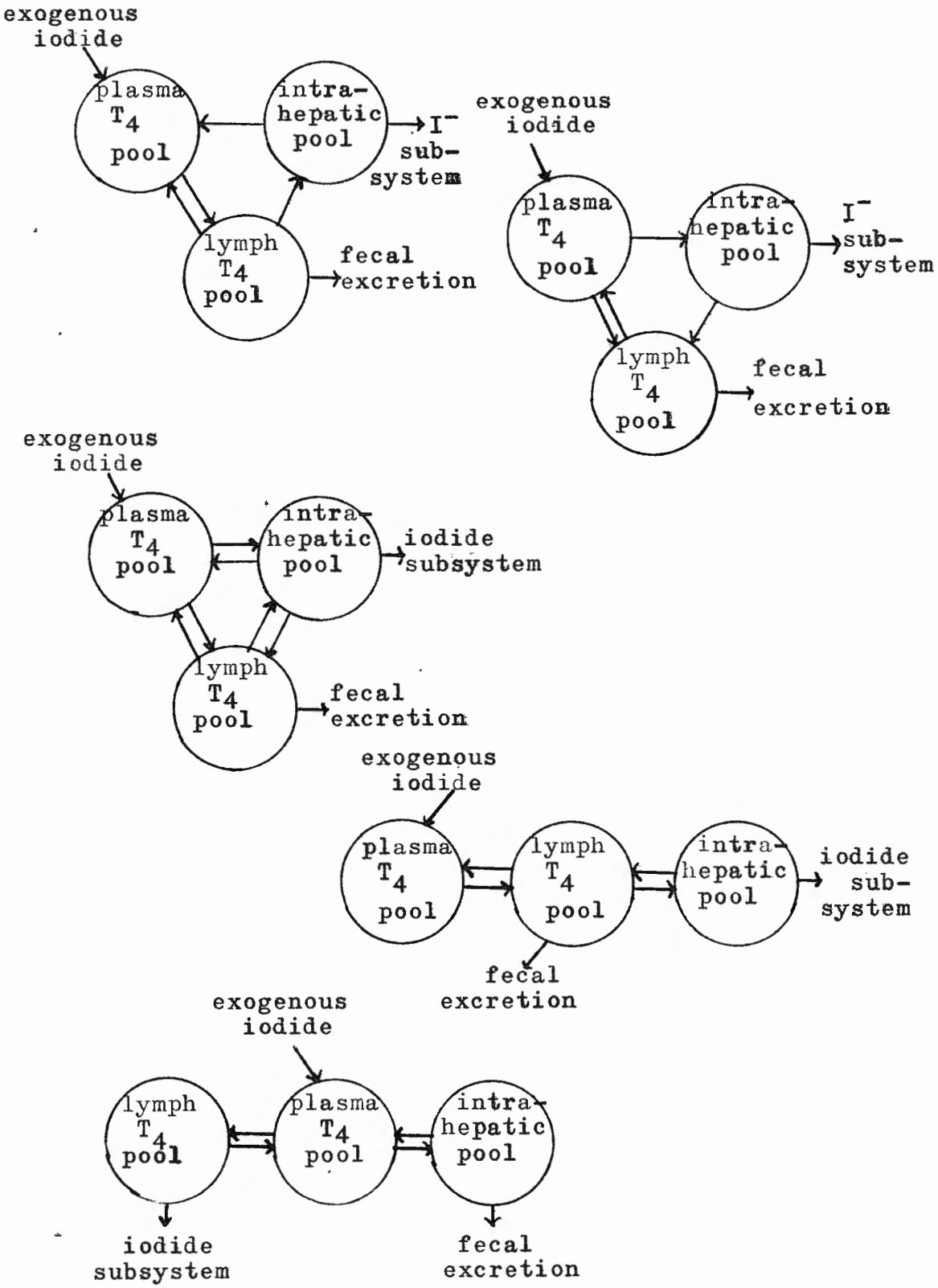


Fig. 5. Schematic Representation of Kinetics of Iodine Metabolism Following Equilibration of Tracer Material with Endogenous Hormone.[34]

The derivation of the mathematical representations between these systems is beyond the scope of this presentation. These systems described above and drawn schematically in Figs. 4 and 5 are discussed here only to give some insight into the complicated metabolic kinetics resulting when a tracer substance is introduced instantaneously into a system. These factors influence the type of curve obtained when the radioactivity in counts per minute is plotted against time (Fig. 3).[32,33,34,35,36,37]

Determination of Turnover Rate and Half-life of T_4.--

Extrapolating a best fit straight line of the linear or final phase back to zero time on the logarithmic plot yields the "initial" radioactivity of the slow phase from the intercept of the slope and ordinate. Utilizing this slope, the half-life in days of the radioactivity is determined by calculating the number of days required for the radioactivity to be one-half of the "initial" administered ^{131}I-T_4. In turn, this value is used to calculate the per cent of administered hormone which is eliminated per day, or turnover rate(k) by the following formula:

$$k = \frac{\log_e 2}{T_{\frac{1}{2}} \text{days}} \times 100 = \% \text{ turnover / day}$$

Normal Values.--

Clinical experience using the radioactive labelled thyroxine in euthyroid patients reveals a mean half-life of the late logarithmic phase(representing thyroxine turnover) in adults from 6.7 to 7.18 days.[17,19,23,33] Mean values have also been reported for patients with hyperthyroidism and myxedema, with mean turnover rates of 2.7 days and 9.4 days respectfully. Fig. 6 illustrates a semilogarithmic plot of normal, hyperthyroid and hypothyroid radiothyroxine disappearance curves.

Other Diagnostic Aids.--

Diagnostic aids used in conjunction with the isotope methods previously described are:

1) Protein Bound Iodine (PBI) - reflects the concentration of circulating thyroid hormone bound to protein. It is predominately a measure of thyroxine concentration and may include iodinated proteins of either endogenous or exogenous origin.[6]

2) Butanol-extractable iodide (BEI) is a procedure whose values closely reflect the PBI level but separates out abnormal inorganic iodinated compounds from the free thyroid hormones. This value more closely reflects the concentration of circulating hormone.[6]

3) Thyroidal radioactive iodine uptake (RAIU) - a test using radioisotopes in which the percentage of

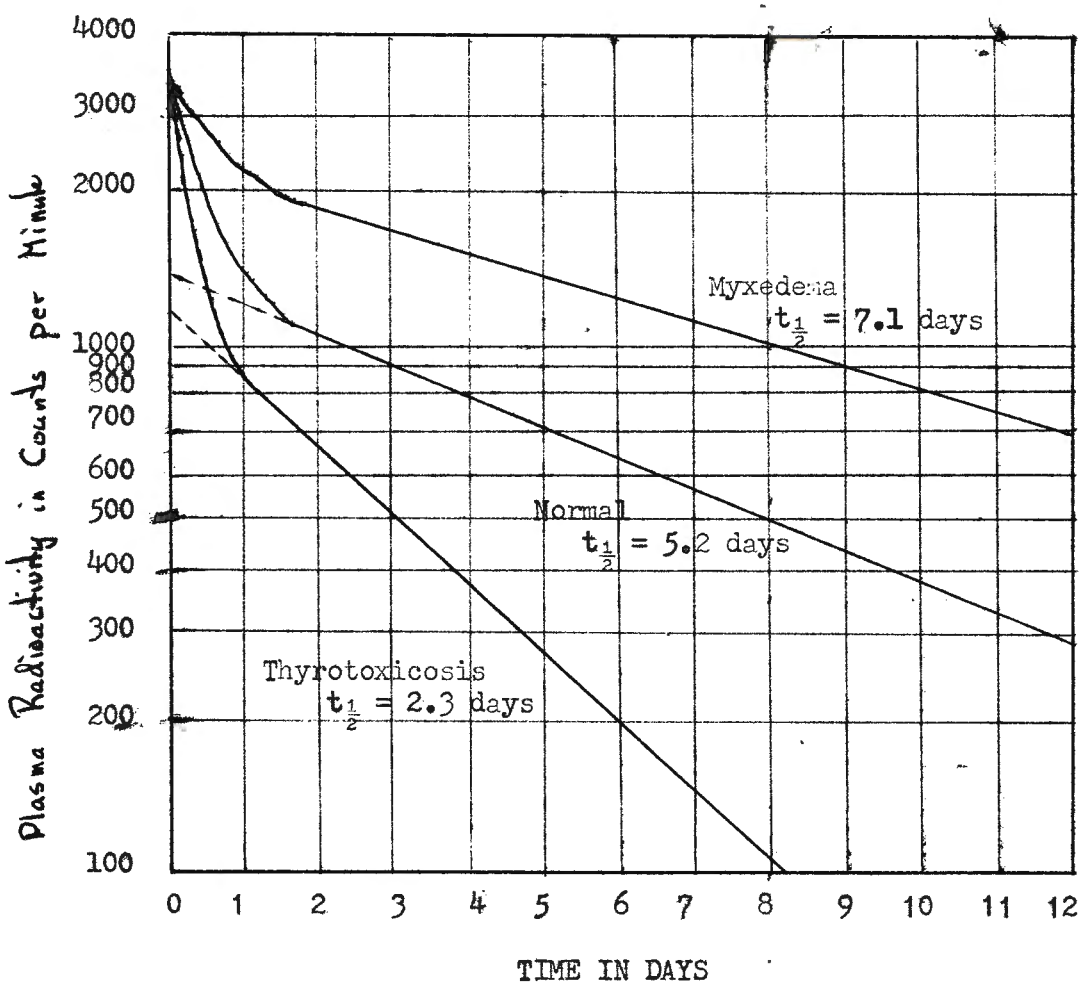


Figure 6. Semilogarithmic plot of selected studies to illustrate kinetic differences in radiothyroxine disappearance curves in myxedematous, normal, and thyrotoxic patients.

administered iodide accumulated by the thyroid gland is determined at specified time periods, usually twenty-four hours.[6]

4) T-3 uptake - a test consisting of addition of ^{131}I-T_3 to whole blood, followed by incubation and then washing of the red cells by standardized conditions. The radioactivity taken up by the cells is then assayed and the results reported as a percentage uptake by the red blood cells after correcting for hemoglobin concentration. These values are then used to estimate the fraction of the total thyroxine in plasma that is not bound to TBP.[9]

5) Free thyroxine - a measure of relative or absolute concentration of serum thyroxine existing at equilibrium as the free or unbound hormone.[6,10]

Review of Published Literature on Clinical States Altering Thyroid Hormone Metabolism and Disposition as Measured by Plasma Half-life of Radioiodine Labeled Thyroid Hormones

Sex.--

The rates of thyroxine turnover and degradation have been compared by several authors[38] as to the effect of sex. Anbar compared results in adults and Oddie[39] and Beckers[40] compared rates in children and came to the conclusion that the rate of metabolism of the thyroid hormones in males and females of the same age group is equal.

Age.--

In the young child during the first week of life Haddad[41] reports there are significant elevations in the PBI and BEI as compared to those of the adult. He shows this as being due to increased thyroxine-binding protein in the serum of the neonate. ^{131}I uptake studies in the neonate reveal values not significantly different than slightly older infants.[41,42] Haddad reports his studies on thyroid hormone metabolism using turnover rates of ^{131}I-thyroxine. His results are a mean half-life of 4.95 days and a fractional turnover of 13.9% per day. This data is then expressed in surface area and body weight parameters to obtain a common denominator for comparison with adults. In children a mean value of 32.0 ugm per meter square per day or 1.29 ugm per kilogram per day is found compared to adult values of 29.4 ugm per meter square per day and 0.75 ugm per kil gram o per day.[41] In his second publication Haddad compares the thyroxine binding capacities in the serum protein of children and adults,

finding a mean of 0.25 ugm of thyroxine per ml in serum of children and a mean of 0.22 ugm of thyroxine per ml in serum of adults. This variation he attributes to increased binding capacity of the thyroid binding proteins in the child, which then decreases the concentration of free or unbound hormone in the blood. [43] Hung reports that euthyroid adolescents use thyroxine at a faster rate ($T_4 t_{\frac{1}{2}}$ of 5.32 days) than the young adult male ($T_4 t_{\frac{1}{2}}$ of 6.83 days) or slower than the child ($T_4 t_{\frac{1}{2}}$ of 4.95 days). He concludes that some factor associated with age per se but not associated with the marked hormonal changes that occur at adolesence is responsible for the changes in thyroxine half-life that occur at that time. Groughs develops this concept further by using the Resin T-3 uptake as a measure of percentage of free thyroxine. In children he reports a mean T-3 uptake of 23.3 ± 2.9% which is significantly higher than a mean adult value of 21.8 ± 2.7%. He postulates on the basis of work done on the binding capacity of protein and his own data with free thyroxine that there is a total lower binding capacity of plasma protein in childhood. This then allows for more free thyroxine which is more readily utilized and metabolized with a subsquent increase in turnover.

On the other side of the spectrum in the older individual. Inada [14] showed that old subjects over 70 years of age have low ^{131}I uptake but PBI values in almost the normal range. Gregerman [45,46] studied the half-life of thyroxine turnover in older subjects and finds the half-time of turnover increases from a mean of 6.7 days in the third decade to

9.1 days in the seventh decade, with no significant increase in mean values of half-life beyond the seventh decade. He also reports a decline in thyroxine degradation rate from a mean of [illegible].7 ugm of T_4 in the third decade to 43.9 ugm of thyroxine in the ninth decade, a decrease of about 50%. Anbar[38] showed that there is no change in the 24 hour ^{131}I uptake over the entire age range. To further evaluate the results of Gregerman,[45] Anbar[38] determined the rate of deiodination and found that the half-life of thyroxine metabolism by deiodination increases from 8 days in the third decade to 13 days in the sixth decade, thus giving a much longer half-life of thyroxine in older patients. Anbar shows that instead of 80% of thyroxine being deiodinated as in young age groups, only 70% is deiodinated in older groups. He concluded that the major alteration in the degradation of thyroxine that changes with old age in a decline in deiodination.[45] Gregerman evaluated the longer half-life of thyroxine when administered to older patients in terms of decreased activity of the patient, alteration of plasma proteins, and changes in the "metabolic mass" of the aging human body, but was unable to establish any significant correlation between these parameters and the thyroxine turnover data.

The work quoted above indicates that the primary difference in comparing the rates of thyroid hormone metabolism in children and adults is an increase in the binding capacity of thyroid binding proteins with age. For this reason the child has more free thyroxine, which is more readily utilized and metabolized. Comparison of young adults

and older subjects shows a further increase in $T_{4}t_{\frac{1}{2}}$. This is ascribed to a decrease in the deiodination route of metabolism, which means the hormone is eliminated from the body slower, thus a prolonged half-life.[2]

Gonadal Hormones.--

As was shown above by Anbar,[33] Oddie,[39] and Beckers,[40] males and females in the same age group show no variation in thyroid hormone metabolic disposition rates. However, the administration of gonadal hormones has been observed to alter certain parameters measuring thyroid hormone concentration and disposition.

Federman[47] has shown that the administration of methyltestosterone to euthyroid adult humans does not significantly alter iodine metabolism as measured by thyroidal uptake of ^{131}I, and thyroid and renal iodide clearances after approximately 50 days of drug administration. There is reported to be a small but significant reduction in the PBI after 28 days of such treatment. The thyroxine binding capacity of the TBG is greatly decreased and the mean free thyroxine concentration is 7.0×10^{-11} M prior to treatment and 10.9×10^{-11} M during treatment. It is further substantiated that there is an increase in free thyroxine and an increase in the fractional rate of thyroxine disappearance from a mean of 13% per day to 19% per day after 28 days of therapy. These authors[47] offer the hypothesis that a fall in the concentration of TBG in the serum is responsible for an increased concentration of free thyroxine and the above changes indicating increased metabolism.

Engbring and Engstrom[48] however do no report as marked a variation from normal as Federman, but do concur that the primary alteration in the metabolism and disposition of thyroid hormones is a decrease in TBG. Braverman and Ingbar[49] studied this problem and observed an increase in the proportion of free thyroxine induced by the mildly androgenic "anabolic" steroid: norethandiolone. They also reported in association with a decrease in thyroxine binding capacity of TBG an increase in the binding capacityof TBPA. The over-all effect of the decreased binding capacity of the TBG however appears to outweigh the increased binding capacity of the TBPA as the TBG binds considerably more hormone than the TBPA.

Estrogen therapy is reported by Engbring and Engstrom[48] to increase the PBI in euthyroid adult patients. They also report an increase in the $T_4 t_{\frac{1}{2}}$ from a mean of 6.9 to 10.6 days in these patients. Conversely to the decrease in the TBG binding capacity observed with the administration of androgenic hormones, the administration of estrogens increases the TBG binding capacity. It is not determined whether there is a quantitative increase in TBG or an increase in the number of binding sites per protein molecule. This condition leads to a decline in concentration of free thyroxine which effects a prolongation of biological $T_4 t_{\frac{1}{2}}$. Dowling[50] reports a prolonged $T_4 t_{\frac{1}{2}}$ with the administration of diethylstilbestrol and estradiol benzoate to "eumetabolic" females. This certainly agrees with the above description of increased binding capacity with a resultant lowered concentration of free thyroxine.

Insulin.--

Insulin is shown to effect the metabolism of thyroid hormones as reported by Rose.[51] Thyroxine metabolism was studied in patients with diabetes mellitus. As a group the patients with more severe disease were noted to have lower levels of serum PBI but the fractional turnover of thyroxine was unchanged in these patients. When insulin was given for at least three weeks, an elevation of serum PBI was observed, and an increased daily thyroxine consumption was reported. This author concluded that the thyroid hormone production was deficient. This may be a compensatory change with a diminished requirement for thyroid hormone in a patient with diabetes mellitus, as the administration of insulin causes an increase in the consumption of oxygen, which then stimulates the thyroid gland to produce hormone at a more rapid rate. As a group the patients with diabetes mellitus were found to have thyroxine turnover study values which were not internally consistent. This lack of consistency was probably due to the severity of the disease at the time of testing a particular patient.

Salicylate.--

Salicylate therapy is reported by Austin[52] and Wolff[53] to increase oxygen consumption up to 33% in euthyroid patients. This observation was followed by an analysis of

thyroid hormone metabolism and disposition in patients with salicylate therapy. In one report, serum PBI was reduced from a mean of 5.5 to 3.8 ugm/100ml by the administration of salicylates. The fractional rate of disappearance of ^{131}I increased from a mean of 11.3% per day to 15.1% per day, and the ^{131}I uptake was reduced to 45% of the control at two hours, 44% at five hours, and 43% at twenty-four hours. Wolff[53] reported that treatment of such patients receiving salicylates with exogenous thyrotropin causes an increase in ^{131}I uptake to normal values, and an elevation of the PBI. Wolf[54] shows that salicylates inhibit thyroxine binding to prealbumin. This displaced free thyroxine is then metabolized at an accelerated rate with an ultimately lower PBI.

Clofibrate.--

Harben and Pittman[55] report in a recent abstract that the administration of clofibrate to reduce hypercholesteremia also alters the metabolism and binding of thyroxine. Liver scans after the administration of the drug show increased hepatic binding of thyroxine and greatly prolonged half-life of thyroxine turnover from a normal mean of 10.7 days to 24.1 days.

Iodine Preparations.--

The effect of increased dietary iodine is reported by Fisher[56] in his study of euthyroid Arkansas subjects who were

given daily iodine supplements. Thyroxine turnover was reported as being unchanged, but radioactive iodine accumulation in the thyroid gland increased while thyroidal radioiodine clearance decreased. DeGroot[57] obtained similar results with the administration of potassium iodide, in amounts of 30 mg per day, which did not significantly alter the peripheral metabolism of labeled thyroxine.

Thyroxine and Analogues.--

Exogenous thyroxine was observed by Oddie[58] to induce a progressive decrease in thyroidal uptake rates which approached zero when 280 ugm of thyroxine was given daily to normal adult men. An associated small but definite increase in PBI levels was reported, and total thyroxine turnover rates were increased approximately in proportion to the elevation of PBI. The fractional daily degradation rate, however, remained relatively constant at this dose level. It thus appears that exogenous thyroxine inhibits the pituitary-thyroid axis by increasing the concentration of hormone in the blood and thus suppressing TSH. The exogenous thyroxine appears to be metabolized at the same rate as endogenous hormone.

D-thyroxine, 3,3',5'-triiodothyronine, 3,3',5'-triiodothyropropionic acid and 3,5'-diiodothyroacetic acid were shown by Pittman[59] to cause changes in radiothyroxine

metabolism, namely, slowing of the disappearance of radiothyroxine from the blood and decrease in deiodination of radiothyroxine. The authors suggest that these analogues compete with the radiothyroxine at all points at which it is metabolized. Schussler and Vance[60] also report that triiodothyronine alters thyroxine metabolism. The per cent of serum thyroxine bound to TBG is increased, TBG capacity is unchanged, and thyroxine turnover rate is increased. The conclusion suggested by these authors is that T_3 stimulates the metabolic disposal of thyroxine which then results in increased catabolism of thyroxine.

Propylthiouracil.--

Propylthiouracil (PTU), an antithyroid drug used extensively in clinical practice is demonstrated by Hershman[61] to slow the degradation rate of thyroxine, possibly by interferring with tissue metabolism of thyroid hormone. Animal studies also suggest that PTU may alter the pituitary suppressive effects and calorigenic action of thyroxine. 6-PTU is shown to alter the rate of radioactive thyroxine disappearance from the serum. The magnitude of this inhibition of thyroxine turnover varies in relation to the level of intrinsic thyroid activity of the subjects studied, as is shown by Furth[62] in hyperthyroid, euthyroid, and hyperthyroid subjects. After 6-PTU administration, thyroxine disappearance rates in patients with active thyrotoxicosis are slowed significantly, and the uptake

of iodine by the thyroid gland is markedly decreased, possibly due to a block in the recycling of iodine by the PTU. Little or no effect on thyroid hormone metabolism or utilization was noted in euthyroid or hypothyroid patients. The authors suggest that PTU acts to decrease deiodination by a constant fraction of the original rate, thus the apparent effect of PTU would be greater in hyperthyroidism in which there is a more rapid rate of thyroxine metabolism.

Tapazole.--

Berson[14] reports no significant increases in degradation or turnover rates in patients prior to or after the administration of tapazole.

Epinephrine.--

In a study reported by Hays[63] ten young males were given repository epinephrine repeatedly for four days during the course of an ^{131}I -thyroxine disappearance study. The plasma ^{131}I-thyroxine disappearance rate slowed abruptly, fecal ^{131}I decreased, urinary ^{131}I excretion decreased slightly. Further studies on binding protein show a serum TBG capacity increase of 14 per cent which began on day two of therapy and continued until one day after therapy. Serum TBPA dropped 11 per cent, and free thyroxine decreased. These changes suggested that the increased binding capacity of TBG is responsible for a de-

crease in ^{131}I-thyroxine metabolism. While this is not fully explained, the authors suggest that the thyroxine binding may be altered in extravascular sites.

Adrenalcortical Steroids.--

Glucocorticoids have been shown to increase the half-life of the ^{131}I-thyroxine turnover in man as is shown by Blomstedt.[64] Orrego[65] showed in liver homogenates that the addition of cortisol inhibits the deiodination of thyroxine, probably due to an inhibitory effect of cortisol on the enzymatic deiodination of thyroxine. This decrease in deiodination of thyroxine would contribute to a flattening of peripheral degradation slope of ^{131}I-thyroxine due to a slower metabolism of the tracer.

Hyperthyroidism.--

Hyperthyroidism is reported by many authors to alter several parameters of thyroid function and metabolism. Turnover of ^{131}I-thyroxine is accelerated to a half-life of two to five days, which suggests an elevated metabolic rate in the peripheral tissues.[14,19,66,67,68,69]

Grave's Disease.--

Ingbar[19] studied the disappearance and rate of peripheral degradation of exogenous ^{131}I-thyroxine in 23 patients with Grave's disease who had been restored to euthyroid status. These subjects displayed an increased fractional rate of turnover (5.2 days) in the peripheral tissues for up to

28 months following establishment of euthyroid state. The mean PBI values were within the normal range. Thus, hypermetabolism per se cannot account for the increase in the fractional turnover rate in these patients.

Euthyroid relatives of patients with Grave's disease were also shown to have abnormalities in their thyroxine metabolism.[69] Thyroxine half-life was significantly reduced from the normal mean of 6.8 ± 0.6 days to 5.7 ± 1.1 days. PBI and Basal Metabolic Rates (BMR) were normal. Thyroidal radioiodine uptakes were significantly greater at 44 ± 8 per cent average for the group as compared to 31 ± 8 per cent in the normal patients without relatives with Grave's disease. Thus, two distinct abnormalities in the metabolism of iodine are found in eumetabolic relatives of patients with Grave's disease: 1) an augmented rate of peripheral degradation of thyroxine, and 2) an increased thyroidal avidity for iodine. At this time no explanation of these observations are available.

In a recent publication, Harban[70] shows that the half-life of radiothyroxine is normal in euthyroid patients exhibiting exophthalmos as seen in Grave's disease. These patients were found to have thyroid function tests in the euthyroid range and no history of hyperthyroidism.

Hypothyroidism.--

Patients with hypothyroidism have also been extensively

studied in all parameters of thyroid function and metabolism. The RAIU is decreased, the thyroidal iodine space is smaller than normal, the PBI and BEI are decreased, and the T-3 (Resin Uptake) is increased. Turnover of ^{131}I-thyroxine is prolonged to a half-life of seven to twelve days. Sterling and Ingbar show that restoration of the eumetabolic state with therapy results in a return of ^{131}I-thyroxine half-life to normal values.

Goiter.--

Beckers[71] evaluates the peripheral metabolism of labeled thyroid hormones in goitrous patients from the Congo. In this population, almost 60% of the persons with goiter have a PBI of less than 4 ugm/100ml. While this would suggest hypothyroidism, only 10% have myxedema. The half-life of thyroxine was found to be 4.4 days with a 15% per day degradation rate. Further studies indicated that the extrathyroidal organic iodine pool is reduced. The author suggests that the increased turnover rate of T_4 and the reduction of extrathyroidal organic iodine pool compensate each other, and despite the reduction of circulating hormone, these patients catabolize an amount of thyroxine greater than would be expected by the level of the protein bound iodine.

Thompson and Wallace[72] report on an investigation of a family with dyshormonogenetic goiter due to dehalogenase

deficiency. These patients mean ^{131}I-thyroxine half-life was 5.1 days, but clinically they appeared hypothyroid, which was confirmed by low PBI values. The authors are unable to explain their unusual findings and have investigated several possible mechanisms with no suitable answer. The TBG capacity is in the normal range while TBPA binding is decreased. TSH was administered to these subjects with no alteration in the ^{131}I-thyroxine turnover.

Nonthyroidal Hypometabolism.--

The term "euthyroid hypometabolism" has been utilized by Kurland[24] to describe patients with a BMR below -20 in association with clinical symptoms suggestive of hypothyroidism but in whom the other customary parameters of thyroid function are within the normal limits. Kurland reports that the half-life of disappearance of ^{131}I-thyroxine is slower (8.3 days) in this group of patients as compared to his controls of 7.18 days. Ryan and Lasker[73] also studied this group and found a prolonged biologic half-life of injected radiothyroxine. They postulate that the most likely reason for the low basal metabolic rate is a disproportion between the mass of metabolizing cells and the mass of fat, and that it is unnecessary to invoke any disorder of thyroid hormone metabolism.

Fever.--

Gregerman[46] reports on thyroxine turnover in patients

experiencing bacterial pulmonary infection, chiefly pneumococcal pneumonia. The acute phase of the illness is characterized by a rapid thyroxine turnover time of 2.3 days. With clinical recovery, the turnover rate reverts abruptly to normal or in a rare case to a slower than normal rate. Wiswell[74] measured ^{131}I-thyroxine and ^{131}I-T_3 concomitantly and showed acceleration of turnover during the acute phase with reversion to normal with recovery. Plasma hormone concentration as measured by PBI and T_4 remained the same throughout acute and recovery phases in humans. Sterling and Chodos[24] concur with the above and observed that thyroid secretion of thyroxine is accelerated during the fever phase, the thyroid thyroxine disposal rate being five-fold that normal during the acute phase of the fever. Shambaugh[75] studied the same situation in the rat with fever induced by subcutaneous injection of five to fifteen organisms of D. pneumoniae. In contrast to the results in humans, a marked decrease in serum PBI and circulating free thyroxine was noted. He also reports a decrease in T_4 binding by the serum protein during fever. Failure of serum TSH to change in response to lower levels of circulating hormone was found and was thought to indicate a decreased pituitary response to alteration in circulating free thyroxine during fever.

Obesity.--

The radiothyroxine turnover and other parameters of thyroid function in obesity were reported by Benoit and Durrance.[78] The BEI values were identical with normal controls at 4.0 ugm/100ml. The mean radiothyroxine biologic half-life in the obese group studies was shortened significantly to 4.3 days with a per cent turnover per day of 16.1. The finding of the shortened half-life was unexpected and mechanically paradoxical with the low metabolic rate frequently noted and the presumed block in cellular utilization of thyroxine in obesity. The authors suspect the explanation for the altered half-life to be due to an increased excretion of thyroxine via the liver and gastrointestinal tract due to a change in hepatic handling of the hormone.

Nephrotic Syndrome.--

The half-life of thyroxine in the nephrotic syndrome is shortened to 3.0 to 4.5 days from a normal range of 5.2 to d.5 days. Thyroid function is described by Rassmussen[79] as "normal", in the sense that the uptake of inorganic ^{131}I by the thyroid is in the normal range. Urinary excretion of thyroxine is greatly increased. This may amount to 25 to 30 per cent of the thyroidal production of thyroxine as compared to approximately ten per cent in the normal human. The amount of thyroxine degraded by the peripheral

tissues is in the hypothyroid range due to less than normal supply of thyroxine reaching these tissues. The transport of thyroxine by plasma proteins appears to be normal. Therefore the primary cause of a shortened thyroxine turnover time is the increased loss of thyroxine through the malfunctioning kidneys.

Pancreatic Steatorrhea.--

Thyroxine metabolism is greatly altered where there is a discrete abnormality in digestive function as in pancreatic steatorrhea. In this disorder, Hiss[80] describes a great increase in the volume of gastrointestinal contents which leads to entrapment of organic iodine secreted in the bile and thereby lost in the feces. Studies show significantly greater quantities of organic iodine in the stool and increased fractional rates of turnover of hormone from 13.0 % per day prior to therapy with "replacement proteolytic enzymes" to 11.8% per day after therapy. Fecal excretion of organic iodine was somewhat reduced after treatment. The thyroxine production by the thyroid gland increases in response to the fecal loss.

Stress.--

Operative stress has been observed by several authors to alter thyroid function. Goldenberg[81,82] reported no alteration in pre- and post-operative PBI values. Four types

of post-operative response are noted by Goldenberg:

1) Increased thyroid activity immediately post-operatively followed by increased adrenocortical activity which is in turn followed by suppression of thyroid function.

2) Increased adrenocortical activity with depressed thyroid activity immediately post operative.

3) Increased thyroid activity post-operatively which is associated with unchanged adrenocortical activity.

4) No change in thyroid or associated adrenocortical activity.

In euthyroid patients who had not experienced recent acute stress or chronic illness was displayed an increased utilization of the labeled T_4 after operation. Much smaller increases were seen in chronically ill patients or those who had recently suffered acute stress. The basic response pattern after operation was shown to be: 1) increased thyroid glandular activity, 2) increased circulating thyroid hormone, and 3) increased peripheral concentration of hormone.

Surks[83] reports an acute reduction in the synthesis of TBPA coupled with a short half-life of this protein as responsible for a rapid drop in TBPA in the post-operative period. Bernstein[84] evaluated the turnover of ^{131}I-thyroxine in patients subjected to surgical trauma by comparing

the turnover to the level of TBPA. Bernstein notes that despite the decrease in TBPA in all his patients, there was also a decreased fractional disappearance of ^{131}I-T_4. He concludes that other factors besides TBPA binding of hormone are present to obscure the influence of falling TBPA levels on the turnover of ^{131}I-T_4.

Human Pregnancy.--

Thyroxine turnover during human pregnancy was described by Dowling[85] who reported that when the net hormonal turnover is expressed in terms of surface area, there is no change between the non-pregnant and pregnant. These values are 35 ugm I^-/24 hours/m^2 and 35.4 ugm I^-/24 hours/m^2 respectively. The PBI values are increased to a mean of 7.4 ugm/100ml due to the increased estrogen associated with the pregnancy. The author concludes that the net thyroxine turnover and hormonal requirements are unchanged in normal pregnancy.

Hepatic Disease.--

Inada and Sterling[86] recently reported in JCI their observation on thyroxine turnover and transport in Laennec's cirrhosis of the liver. Inspite of great irregularity in thyroxine half-lives, the absolute thyroxine iodine removal rates are all normal regardless on the severity of the disease. $T_4 t_{\frac{1}{2}}$ mean values in the control group were 7.7 days and 7.2 days in patients with cirrhosis. The PBI was not

altered with a value of 5.0 ugm/100ml in the control group and a mean value of 5.1 ugm/100ml in the patients with cirhosis. The major alterations appeared to be in the serum proteins including the thyroxine carriers. The TBG concentration was 19.7 in the control group and 20.5 in the patients with cirhosis. The TBPA was decreased by approximately one-third from a normal of 265 ugm/100ml to a value of 95 in the advanced cirrhosis patient. The decreased TBPA capacity was due to impaired synthesis in the diseased liver. The biological half-life shows good correlation with the TBG capacity but not with the TBPA capacity. It is suggested that the diminution in TBPA capacity is compensated for by the normal to elevated TBG binding capacity. Free thyroxine levels also flucuate markedly, as do the biological half-lives. However the absolute hormone disposal is normal in all patients studied.

Thyroid gland function tests have been reported by Friss[70] as normal in patients with hepatitis. The thyroxine half-life was shortened in all six patients while the total thyroxine degraded daily was increased. The author proposed the impaired liver function in this disorder as the cause for the shortened half-life and increased degradation. A larger amount of thyroxine was excreted in the feces as the diseased liver is unable to retain the hormone to the same extent as the normal organ, therefore

more is passed via the bile into the feces. This concept parallels that of Oppenheimer[87] who after external measurements over the hepatic area and studies involving hepatic biopsies indicate that the liver is a very important but probably not the sole component of the intracellular compartment of extrathyroidal thyroxine. In patients with liver disease, he reports decreased intracellular space and impaired permeability characteristics. The normal intrahepatic intracellular thyroxine level is approximately 78% of the total thyroxine with the remaining 22% apparently in the kidney. Thus, with the large portion of intracellular thyroxine being in the liver, impaired liver function can easily allow a release and subsequent loss of this hormone.

Altitude.--

Surks[88] measured plasma total and free thyroxine concentration, thyroxine turnover, catecholamine excretion and oxygen consumption in five young males at an altitude of 14,100 feet for eight days. Thyroxine degradation is observed to increase during the first three days at high altitude and thereafter to remain slightly elevated. Basal oxygen consumption increased from 125 to 147 ml/minute/m^2 on the first day at high altitude and then progressively decreased toward the control value. Plasma total and free thyroxine concentration and norepinephrine

excretion were not altered during the first two days at high altitude but then increased continually for the remainder of altitude exposure. The parallel changes in both sympathetic activity and plasma free and total thyroxine concentration at altitude are noteable. The more delayed onset of the increases of sympathetic activity and plasma thyroxine suggests an adaptive response to the environmental stress imposed by high altitude. The authors suggest that these hormonal changes play an important supportive role in maintaining the integrity of cellular metabolism in situations in which it may be compromised.

Malignant Tumors.--

Sterling and Chodos[24] made a reference to four cases of leukemia with fever which they described as "hypermetabolic without endocrine disease." Thyroid hormone degradation rates in their patients were somewhat lower than the thyrotoxic patients but still significantly greater than normal with a mean value of half-life of 13.7%/day and a normal PBI value.

Oppenheimer, et al,[4] in 1963, report on the binding of T_4 by serum protein as altered in nonthyroidal illness. Their group of patients included several with malignant disease. In general, these patients with the most pronounced thyroxine binding protein abnormalities had marked systemic manifestations including fever, weight loss, and

malnutrietion. An increased T-3 uptake is reported in these patients with metastatic disease. These authors report an actual fall in TBPA with a subsequent decrease in T_4 binding. The possibility of catabolism of the protein in severe wasting disease is mentioned, but additional studies show such is not always the case. Further study is currently being undertaken by these authors to establish the role of thyroxine binding proteins (especially TBPA) in debilitating disease states.

Animal studies showing the effect of malignant tumor on thyroxine metabolism and thyroid function in the rat, were reported by Galton and Ingbar.[90] It was concluded that the changes in thyroid hormone economy in tumorous animals are secondary to decreased protein binding of T_4. It is not known whether this represents a nonspecific response to illness or a specific effect of the tumorous state. The PBI is considerably reduced, deiodination of T_4 is increased with an associated reduction in the concentration of ^{131}I-T_4 in the serum. The clearance of T_4 from plasma is greatly increased. The thyroid gland studies indicate hypofunction as shown by greatly decreased rates of uptake of iodide by the gland.

Pastorelle[89] reported on the acute plasma disappearance time of radioactive thyroxine in patients with cancer. He reports that cancer is associated with decreased thyroid

function with a slower uptake of ^{131}I in the RAIU. Possible causes of these alterations are that cancer induces hypothyroidism, existing hypothyroidism provides a favorable developmental environment for malignant disease, or that the malignant state changes the intra- or extrathyroidal metabolism of inorganic iodide ore thyroxine. He studied these alterations on the basis of acute plasma disappearance time of T_4 which is related to the slope of the clearance curve during the first hour after injection of the labeled hormone. Normal values for acute phase $t_{\frac{1}{2}}$ are 73 minutes. Patients with cancer are classified into three categories on the basis of acute plasma disappearance time and liver function tests: Category A includes patients with normal disappearance times and normal liver function tests; Category B, patients with prolonged disappearance times and normal liver tests; and Category c, patients with prolonged disappearance times and abnormal liver function tests. This author suggests that the alteration in disappearance times in carcinoma is a function of the degree of liver involvement, as the patients with liver disease are unable to trap T_4 from the blood as quickly and thus manifest a prolonged disappearance time.

Summary of Literature Review on Clinical Situation Altering Thyroid Hormone Metabolism

Condition	PBI (ug/100 ml)	$T_{4}t_{\frac{1}{2}}$ (days)	Turnover rate (% per day)	Author
Age 3 - 9	6.09	5.4	13.9	40,41,42
4 - 15		6.0	12.2	40
3 - 14		5.3	13.0	38
15 - 17		5.5	12.4	44,45
Young Adult	4.0 - 8.0	5.4		38
41 yr		10.5		
54 yr		13.1		
74 yr		13.1		
Methyl testosterone	Pre 4.9 Post 3.7		13 19	47
Norethandiolone	4.5		10.9	49
Estrogen	Pre 6.9 Post 10.6			48
Diabetes				
low calorie	6.0	6.5		51
gen diet	5.7	6.2		51
Salicylate	Pre 5.5			53,53
Potassium-iodide	Post 3.8 12.4	Pre 16.7	Post 17.8	57
Hyperthyroidism	11.1	2 - 5	21.7	14,69
Hypothyroidism	1.7	7 - 12	15	70,73

Condition	PBI	$T_4 t_{\frac{1}{2}}$ (days)	Turnover rate (% per day)	Author
Treated Grave's disease	normal	5.2		19
Relatives of patients with Grave's Diseass	normal	5.7		72
Dyshormonogenetic goiter		5.1		74
Euthyroid Hypometabolic	normal	8.3		24,75
Fever	normal	2.3		46
Obesity		5.5	16.1	78
Nephrolic syndrome		3.0		79
Pancreatic steatorrhea	5.3	6.0	13.0	80
Pregnancy	7.4			85
Cirrhosis	5.1	7.2		86

Preliminary Considerations of Plasma Disappearance Rates of Radioactive ^{131}I-Thyroxine in Patients With Malignant Disease

Background.--

The disappearance curves of ^{131}I-Thyroxine and other parameters of thyroid function and disposition, as altered by various clinical situations have been presented previously in this paper. Utilizing the concepts of tracer materials to study the kinetics of thyroid hormone utilization and metabolism, a preliminary report of an investigation involving the long term alterations of thyroid hormone metabolism and utilization is presented on patients with malignant disease.

Premise of Study.--

The purpose of this study is to determine the amount and type of change observed in thyroxine turnover and disposition in patients with various types and stages of malignant disease. It is expected that utilization of thyroxine might be altered in patients with malignancy without regard to associated fever, drug therapy, generalized tissue catabolism, or caloric deficiency. Findings by other investigators [4,31,89] indicated that cancer is associated with decreased thyroid function, one possible cause of which is that the malignant state changes the intra- or extra-thyr-

oidal metabolism of inorganic iodide to thyroxine.[31] Many tumors of non-endocrine origin are now known to elaborate humoral substances which stimulate hormonal action,[90] including thyroid hormone utilization and metabolism.[4,31,89] Pastorelle[31] showed that thyroid hormone utilization is altered in the acute phase due to disturbances in hepatic binding of thyroxine. He showed the alterations in hepatic binding to be roughly proportional to the amount of disruption of hepatic function by the malignant process. To investigate further the effects of malignant disease on thyroid hormone utilization and metabolism, a series of experiments were designed to measure plasma clearance rate of ^{131}I-thyroxine over a period of several days in patients with various types and stages of malignancy, but with no other clinical situations previously described which are known to alter thyroid hormone clearance rates.

Materials and Methods.--

Seven patients with histologically verified malignant disease (leukemia, lymphoma, carcinoma or sarcoma) at various stages but without evident attended infection or thyroid disease have thus far been chosen from the general ward population in the Omaha Veterans Administration Hospital. Five patients with non-malignant, non-febrile diseases, and euthyroid state have been chosen as age

matched controls. Body weights were matched and nutrietional states were similar for both groups studied. Most patients were ambulatory. None were receiving radiation therapy, chemotherapy, or medications known to alter thyroid hormone metabolism at the time of testing. None had received surgical treatment for at least one month prior to testing.

To eliminate patients with clinical states known to give spurious results on thyroxine utilization, a complete history and physical was performed on each patient with special emphysis on type of tumor, date of diagnosis, method of diagnosis, therapy and medications, abnormalities in the thyroid, gastrointestinal tract including liver, renal, metabolic, and weight changes.

Laboratory data was then obtained to aid in eliminating metabolic, hemopoietic, hepatic, renal or thyroid abnormalities. The thyroid gland and hormones were studied extensively to ascertain any abnormalities in function which may have been due to intra- or extra-thyroidal changes induced by the malignant process. The parameters measured include PBI, free T_4, T-3 (Resin-uptake) and RAIU after completion of the series of plasma collections.

Tracer amounts of ^{131}I-labeled L-thyroxine were obtained from Abbott Laboratories in North Chicago, Illinois. The tracer is chemically synthesized L(-)-thyroxine which

is tagged with radioactive iodine in the 3' position and prepared as a sterile solution which contains 50% propylene glycol in water. Intravenous injection was made using glass tuberculin syringes after which corrections for loss of radioactivity due to adherence to glass were made. The amount injected was 40 to 70 microcuries per milligram of thyroxine. Heparinized blood samples were drawn daily for ten days at approximately 10:00 CDT, plasma separated and refrigerated in plastic tubes until the series on that particular patient was completed. Correction for physical decay was made by simultaneous count of a standard sample of radiothyroxine prepared at the time of initial administration of the tracer. The plasma activity was assayed in a well-type scintillation counter which records approximately one million counts per minute per microcurie of ^{131}I by standard techniques of the radioisotope laboratory of the Omaha Veterans Administration Hospital.

Calculations.--

The disappearance of plasma radioactivity was exponential after initial mixing and equilibration (24 to 48 hours) and was expressed as the slope of the line which gave the best fit of the data. Extrapolation to zero time gives the "initial" radioactivity, from which the length of time (days) required for the plasma radio-

activity to diminish by 50% is determined. This value is the half-life of disappearance of plasma thyroxine, ($t_{\frac{1}{2}}$). From this value the percentage of thyroxine turned over per day is calculated by:

$$k = \frac{\text{Inz} \times 100}{t_{\frac{1}{2}}} = \frac{0.693}{t_{\frac{1}{2}}} \times 100.$$

Results.--

The values for the control subjects (Table 3) and values for the patients with malignancy (Table 4) show slight changes in half-life of radiothyroxine. The mean value for the control subjects is 6.5 days, compared to 6.2 days for the patients with malignancy. Other parameters, however, do not agree as closely. The PBI is measured in the normal subjects in 7.3 ugm/100ml compared to 4.17 ugm/100ml in the test patients. This discrepency may be due to one highly abnormal value in W.S., which is presumed to be due to non-hormonal iodine, as the T-4 value is normal. Eliminating this PBI determination from the series gives a mean value of 5.8 ugm/100ml, which is still significantly higher than the tumor group. The T_4 by column which measures predominately thyroxine, revealed a much higher level of serum thyroxine in the controls (4.5 ugm/100ml) as compared to the tumor group

Table 3. Thyroid Function Studies in Patients Without Malignant Disease

Subject	PBI (ug/100 ml.)	T_4 (ug/100 ml.)	T-3 Resin Uptake	$t_{\frac{1}{2}}$ (days)	k BSP (%)	(%)	Chol (mg/100 ml.)	alb (%)	α_1 (%)	α_2 (%)	β (%)	γ (%)	alk phos (units)
M.A.	4.3	3.7	31.8	5.0	13.9								
W.S.	13.4	3.6	39.6	6.3	11.0	3.5	150	58.6	1.4	9.4	11.3	19.0	3.7
R.F.	7.7	6.3	31.2	5.8	11.9								
R.E.	5.4	4.3	37.9	8.3	8.4								
W.B.	5.7	4.6	37.6	7.2	9.6								
total	36.5	22.5	178.1	32.6	54.8								
mean	7.3	4.5	35.6	6.5	10.9								

Table 4. Thyroid Function Studies in Patients With Malignant Disease

Subject	PBI (ug/100 ml.)	T_4 (ug/100 ml.)	T-3 Resin Uptake	$t_{\frac{1}{2}}$ (days)	k (%)	BSP (%)	BUN (mg/100 ml.)	Protein alb (%)	(%)	(%)	(%)	(%)	alk phos (units)
W. M.	4.9	3.6	35.2	6.1	11.4	2.3	7.9						
R. M.	5.4	4.1	37.4	5.8	11.9	7.8	13.0	49.1	3.8	10.2	14.0	22.1	2.8
W. N.	6.5	6.8	30.2	8.2	8.5	13.2	9.0						12.9
A. S.	4.4	3.4	32.0	9.1	7.6	6.1							8.1
R. S.	3.1	2.7	39.0	3.6	19.2		28.0	53.8	3.8	9.0	13.3	20.0	6.3
D. A.	3.7	2.9	40.8	4.5	15.4		36.0	61.4	4.7	9.5	14.3	9.9	
total	28.0	20.5	247.4	37.3	73.8	29.4	94.9	164.3	12.3	28.7	41.6	52.0	38.8
mean	4.7	3.9	35.8	6.2	12.3	8.3	18.8	54.8	4.1	9.6	13.7	17.3	7.8

(3.9ugm/100ml). The T-3 (Resin uptake) is essentially identical in both groups, indicating that the binding capacity of the thyroid binding proteins is essentially the same in both groups. As expressed by the k value, the per cent of the radiothyroxine turned over per day is increased from a mean of 10.95% in the control to 12.3% in the patients with malignancy. Further analysis of the small series collected thus far reveals no correlation between thyroxine turnover and hepatic function alteration as measured by the BSP and serum alkaline phosphatase levels. A pattern, however, may be evident with increased turnover per day with lower levels of gamma globulins, However, a larger series is needed to determine if this is a significant correlation.

Discussion.--

A much larger series will be required to determine the alterations in thyroid hormone utilization and metabolism as influenced by the malignant state. As a total group, the patients with malignancy show alterations in several parameters of thyroid function measurement, especially in the PBI with much lower values, T_4 with lower values, and per cent turnover per day, which shows larger amounts of thyroxine utilized per day.

Further studies are needed to evaluate whether the changes above are due to decreased hepatic binding with

subsequent loss of hormone or alterations in the thyroid hormone binding protein capacity. This change in the binding capacity may be due to an absolute decrease in the number of binding sites as would be shown by decreased concentrations of the binding proteins or a decrease in the binding capacity of normal concentrations and ratios of plasma thyroid binding proteins. Studies of free thyroxine and the turnover of absolute quantities of free thyroxine may aid in clarification of the question of alterations in thyroxine utilization and degradation in malignancy. Future studies involving larger numbers of subjects will allow observations to be made in various possible stages of malignancy and with progression of the disease in a given patient. In addition, alterations induced by therapy may be observed to determine the effect of the amount of involvement of the person's body and physiology necessary to alter the normal thyroid hormone utilization, metabolism, and disposition.

Larger studies are also needed to compare the various types of malignancy (leukemias, carcinomas, sarcomas, and lymphomas) and their effects on the parameters measured above.

The above mean values and trends indicate that thyroid hormone metabolism may be altered in patients with malignancy. Thus is indicated a need for further investi-

gation with various modifications listed above.

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