Metabolic Clearance and Production Rates

of Human Thyrotropin

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ABSTRACT Metabolic clearance (MCR) and production rates (PR) of human thyrotropin (hTSH) were determined by the constant infusion to equilibrium method 57 times in 55 patients. 16 control patients had a mean hTSH MCR of 50.7 ml/min. The mean hTSH MCR was significantly ($P < 0.02$) higher in 19 euthyroid men (51.6 ml/min) than in 12 euthyroid women (43.0 ml/min), but this apparent sex difference disappeared when the MCR were corrected for surface area, 25.8 (men) versus 25.2 ml/min per m^2 (women). Hypothyroid patients had significantly ($P < 0.005$) lower hTSH MCR (30.9 ml/min), and hyperthyroid patients had significantly ($P < 0.05$) higher hTSH MCR (60.9 ml/min) than controls. The hTSH MCR in patients with "decreased thyroid reserve" (40.9 ml/min), hyperfunctioning thyroid nodule (53.8 ml/min), and "empty sella syndrome" (46.6 ml/min) were not significantly different from controls. The mean hTSH PR in controls (104.3 mU/day) was significantly ($P < 0.005$) different from that in patients with "decreased thyroid reserve" (956 mU/day), hypothyroidism (4,440 mU/day), hyperthyroidism (< 43.9 mU/day) and a hyperfunctioning thyroid nodule (< 38.7 mU/day). In primary hypothyroidism intravenous triiodothyronine therapy (50 μg/day) for 10 days decreased the hTSH PR (from 4,244 to 2,461 mU/day) before changes in the hTSH MCR (from 33.1 to 33.7 mU/day) were observed.

These studies have demonstrated that changes in the serum concentration of hTSH are mainly due to altered pituitary hTSH secretion with only a minor contribution from the change in hTSH MCR.

INTRODUCTION

The introduction of methods for measuring human thyrotropin (hTSH) [1] in serum (1–5) have made it possible to define the thyroid and pituitary interrelationships in various thyroid disorders. However, despite the common use of the serum hTSH concentration, little information exists on metabolic clearance rates (MCR) and production rates (PR) of hTSH in health and disease. In 1962, Bakke, Lawrence, and Roy (6) administered bovine TSH intravenously to euthyroid and hypothyroid patients, determined the half-life of the serum bTSH by bioassay, and estimated production rates of hTSH to be 260 USP mU/day in the former and approximately 2,600 USP mU/day in the latter. In 1967, Odell, Utiger, Wilber, and Condliffe (7) injected [131I]hTSH intravenously as a single bolus in tracer quantities and followed the disappearance of labeled hormone by antibody precipitation. MCR were 42.5 ml/min in euthyroid and 36.3 ml/min in hypothyroid patients. The calculated hTSH production rates were 165.2 mU/day and 1,033.1 mU/day respectively, in terms of human TSH reference standard A. In 1971, Beckers, Machiels, Soyez, and Cornette (8) utilized a similar single injection technique and found no statistically significant difference in the MCR of euthyroid (56.2 ml/min), hyperthyroid (60.6 ml/min), or hypothyroid (62.8 ml/min) patients. Furthermore, the calculated production rates in this study suggested that hyperthyroid patients had higher production rates of hTSH (517.2 mU/day) than euthyroid patients (419.1 mU/day).

In an attempt to elucidate this problem further and to resolve these discrepancies, we have measured the

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[1] *Abbreviations used in this paper:* hTSH, human thyrotropin; MCR, metabolic clearance rates; PR, production rates, RaI, radioiodine; T_4, thyroxine; T_3R, triiodothyronine resin uptake; TT_3, total triiodothyronine; TT_4, total thyroxine.
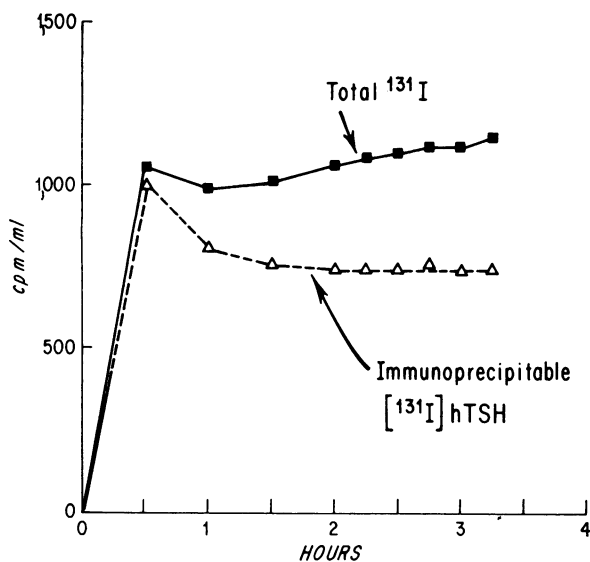
FIGURE 1 Total ^{131}I (■) and immunoprecipitable [^{131}I]-hTSH (△) during constant infusion of [^{131}I]hTSH. Apparent equilibrium was achieved between 2 and 3½ h.

MCR of hTSH in various thyroid disorders by means of the constant infusion to equilibrium method of Tait (9). Further, we have measured the endogenous hTSH concentration and calculated its PR using a sensitive radioimmunoassay capable of differentiating normal from low hTSH levels in unconcentrated sera (5).

METHODS

Preparation of [^{131}I]hTSH. Highly purified hTSH was obtained for labeling from the National Pituitary Agency. hTSH was labeled with ^{131}I to specific activities of 25–50 μCi/μg by the method of Hunter and Greenwood (10). Immediately after iodination the [^{131}I]hTSH was separated from aggregated products of iodination and inorganic iodide on a G-100 Sephadex column (1.5 × 90 cm). Approximately 0.25–1.0 μg (10–50 μCi) of purified [^{131}I]hTSH was diluted in 80 ml of 0.9% normal saline and 1% human serum albumin. This solution was sterilized by Millipore filtration and confirmed by bacteriological studies. The interval between iodination and infusion varied between 3 and 10 days.

Measurement of [^{131}I]hTSH. [^{131}I]hTSH was separated from serum or infusate by a double antibody system in which 0.8 ml of serum or 0.1 ml of infusate was incubated with excess rabbit anti-hTSH serum at a final dilution of 1:100 for 24 h at 4°C. Subsequently, goat anti-rabbit gamma globulin was added, and the reaction mixture was incubated for another 24 h at 4°C. The samples were centrifuged, and the supernate was decanted. Total and immunoprecipitable radioactivity were determined on duplicate samples in a standard autogamma spectrometer after subtraction of background counts in control tubes. All tubes were counted to at least 10,000 counts to yield a counting error of ±1%. 90–100% of the total radioactivity in the infusate was precipitable by this method. Appropriate vol-

ume corrections were made so that radioactivity was expressed as counts per minute per milliliter.

Infusion of [^{131}I]hTSH and collection of sera. 80 ml of infusate contained 0.9% normal saline, 1% human serum albumin, and approximately 0.25–1.0 μg [^{131}I]hTSH. To reduce the time necessary to reach equilibrium, 20–30 ml of infusate was initially injected as a bolus. After 15 min the remainder was infused at a constant rate (0.1765–0.1908 ml/min) for 3–4 h. At this time, apparent equilibrium was reached as defined by that time following which subsequent measurements of immunoprecipitable labeled hTSH levels showed no variation that exceeded ±10% of the mean [^{131}I]hTSH concentration during a 1-h period (Fig. 1). During this period of apparent equilibrium, at least three blood samples were collected at 15-min intervals, and the serum was separated for determination of [^{131}I]hTSH content.

Determination of hTSH MCR. At apparent equilibrium the immunoprecipitable [^{131}I]hTSH was averaged in at least three duplicate serum samples and expressed as counts per minute per milliliter. The [^{131}I]hTSH infusion rate was determined by multiplying the content of [^{131}I]hTSH in the infusate by the infusion rate, and this figure was expressed as counts per minute per minute. The MCR of [^{131}I]hTSH was then determined by the formula (9, 11):

$$MCR\,(ml/min) = \frac{\text{Infusion rate } [^{131}I]hTSH\ (cpm/min)}{\text{Serum concentration } [^{131}I]hTSH\ (cpm/ml)}$$
$$\text{at apparent equilibrium}$$

Determination of endogenous hTSH. The endogenous serum concentration of hTSH was determined by a modification (5) of the radioimmunoassay method of Odell, Wilber, and Utiger (1) and similar to that recently reported by Patel, Burger, and Hudson (4). Values for normal subjects were 1.67±0.68 μU/ml in terms of hTSH reference Standard B with approximately 90% (47 of 52) of normals having detectable levels and most (39 of 41) hyperthyroid patients having undetectable levels, i.e., less than 0.5 μU/ml.

Determination of endogenous hTSH PR. The PR of hTSH was calculated by the product of the endogenous serum concentration of hTSH and the MCR of [^{131}I]hTSH with the following formula (7, 9):

hTSH PR (μU/min) = [hTSH] (μU/ml)
   × hTSH MCR (ml/min)

Subsequently, all values for production rates were expressed as milliunits per day.

Patients. There were 31 patients who were clinically euthyroid. 16 of these patients had no history of thyroid or pituitary disease and normal levels of total thyroxine (TT$_4$), free thyroxine (free T$_4$), total triiodothyronine (TT$_3$), T$_3$ resin uptake (T$_3$R), RaI uptakes, and hTSH. The circulating levels of TT$_4$, free T$_4$, and TT$_3$ were all performed by competitive protein binding assays and equilibrium dialysis techniques (5).

The 16 patients included 10 men and six women and served as the control group. The other 15 patients, judged to be clinically euthyroid, had historical evidence of either thyroid or pituitary disease but had normal levels of TT$_4$, free T$_4$, and TT$_3$, and T$_3$R. These 15 patients were specifically included to provide a greater number of MCR determinations in patients with normal levels of circulating thyroid hormones and included the following: four patients with the empty sella syndrome documented by pneumoencephalography who were taking no therapy; four patients with a hyperfunctioning thyroid nodule, and seven

TABLE I
hTSH Serum Concentrations, MCR Rate and PR in Control Subjects

Patient	Age	Sex	Surface area	Immuno-precipitable cpm infused	Immuno-precipitable cpm at apparent equilibrium ±SD	Serum hTSH	hTSH MCR*	hTSH PR
	yr		m*	cpm/min	cpm/ml	µU/ml	ml/min	mU/day
R. O.	34	M	2.15	64,475	747±10	1.1	86.3	137
W. O.	54	M	2.10	36,873	622±14	1.1	59.3	94
W. M.	47	M	1.97	43,074	893±11	1.0	48.2	69
W. M.	49	M	2.08	48,499	872±30	1.0	55.6	80
P. S.	17	M	2.20	108,384	2,021±18	1.0	53.6	77
W. W.	36	M	2.40	42,288	779±24	2.2	54.3	172
J. S.	26	M	1.81	34,208	858±42	2.1	39.9	120
R. B.	26	M	1.77	37,760	875±27	2.4	43.2	150
A. M.	30	M	2.00	24,688	307±15	1.25	80.3	145
J. D.	29	M	1.95	60,597	1,312±40	2.15	46.2	143
R. J.	65	F	1.63	49,493	954±34	0.75	39.5	43
B. D.	31	F	1.58	85,991	2,866±40	0.70	30.0	30
H. N.	54	F	1.53	25,946	818±17	1.7	31.7	78
J. B.	17	F	1.65	29,388	680±85	1.8	43.2	112
S. R.	18	F	1.94	43,081	709±19	1.6	60.8	140
B. S.	31	F	1.73	53,723	1,370±55	1.4	39.2	79
Mean±SD						1.45±0.55	50.7±15.6	104.3±41.4

* MCR data in this table are expressed as milliliters per minute in order to facilitate comparison with previous studies (7, 8). Our studies suggest that it may be more appropriate to express MCR as ml/min per m² (see Fig. 2 and text).

patients classified as miscellaneous; one patient with euthyroid Graves' disease taking no therapy, three patients with a pituitary tumor, only two of whom were taking replacement doses of thyroid hormone (90–120 mg dessicated thyroid), and three patients, evaluated 6–12 months after radioactive iodine therapy of hyperthyroidism, who were taking no therapy. In one patient with a hyperfunctioning thyroid nodule and one patient with a pituitary tumor, the MCR determinations were performed twice. Thus, a total of 33 MCR determinations were performed in 31 patients with normal levels of circulating thyroid hormones. In addition, there were 12 patients with primary hypothyroidism as defined by classical signs and symptoms of hypothyroidism, a low TT₄, free T₄, TT₃, T₃R, RaI uptake, and an elevated serum TSH level. Five of the patients with primary hypothyroidism were studied again after 10 days of intravenous triiodothyronine therapy (50 µg/day). There were six patients with classical hyperthyroidism as defined by classical signs and symptoms of hyperthyroidism, TT₄, free T₄, TT₃, T₃R, and RaI uptake. There were six patients with "decreased thyroid reserve" who had either Hashimoto's thyroiditis or Graves' disease previously treated with radioactive iodine. These six patients had low-normal levels of TT₄, free T₄, TT₃, T₃R, RaI uptakes, and an elevated endogenous serum hTSH concentration, but did not have signs and symptoms of hypothyroidism. They were further characterized by a subnormal response to exogenous intramuscular bovine TSH (10 U/day for 3 days).

RESULTS

MCR of hTSH. Determination of the MCR of hTSH depended on the [¹³¹I]hTSH concentrations be-

ing at equilibrium at the time of sera collection. Fig. 1 shows a typical infusion of [¹³¹I]hTSH; apparent equilibrium was reached between 2 and 4 h. For this reason at least three serum samples were taken in all infusions between 3 and 4 h. The mean [¹³¹I]hTSH concentrations in control patients are expressed with standard deviations in Table I. A total of 33 clearance rate determinations were performed in 16 control patients and 15 clinically euthyroid patients with a past history of thyroid or pituitary disease with a mean MCR of 48.0±13.4 ml/min. The 19 men had a mean MCR of 51.6±14.9 ml/min, significantly different (P < 0.02) from that of the 12 women with a mean MCR of 43.0±9.1 ml/min. This apparent significant sex difference disappeared (Fig. 2) when the MCR was expressed per square meter of surface area, whereby the males had a MCR/m² of 25.8±6.9 ml/min per m² and the females had a MCR/m² of 25.2±4.3 ml/min per m², which was not significantly different (P = 0.4).

Because of this apparent sex difference, all further results are expressed as both MCR and MCR/m². The 16 control patients had a mean MCR of 50.7±15.6 ml/min or MCR/m² of 26.9±7.9 ml/min per m²; 12 primary hypothyroid patients had a MCR of 30.9±8.3 ml/min or 18.7±3.3 ml/min per m²; 6 hyperthyroid patients had a MCR of 60.9±4.9 ml/min or MCR/m² of 31.1±3.6 ml/min per m². The control patients had
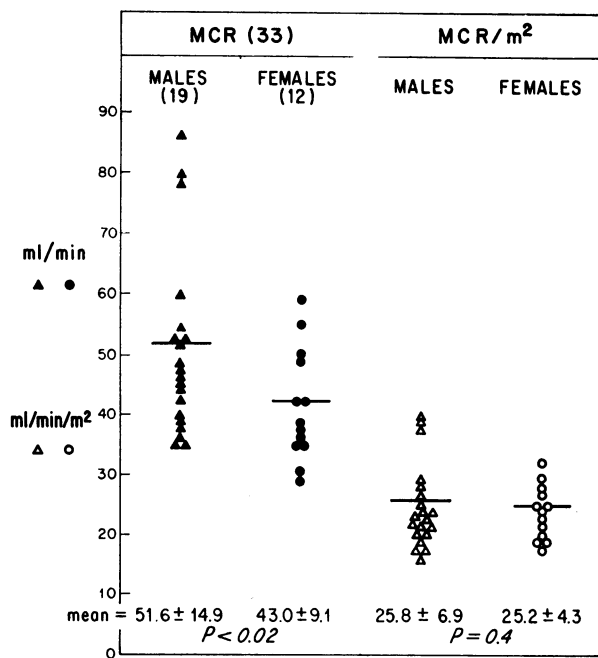
FIGURE 2 33 determinations of hTSH MCR in 19 men and 12 women. The apparent significant sex difference in the MCR (●, ▲) is resolved when the data is expressed as MCR/m² (○, △).

MCR or MCR/m² that were significantly different from hypothyroid ($P < 0.005$) and hyperthyroid patients ($P < 0.05$). Six patients with decreased thyroid reserve had a mean MCR of 40.9±7.3 ml/min or 23.3 ml/min per m²; four patients with hyperfunctioning thyroid nodules had a MCR of 53.8±19.9 ml/min or 29.4±8.3 ml/min per m²; four patients with the empty sella syndrome had a MCR of 46.6±8.2 ml/min or 24.5 ml/min per m² (Table II).

Correlation of hTSH MCR with serum thyroid hormone concentration and creatinine clearance. The MCR and MCR/m² of hTSH of all patients were related to the serum TT_4 concentration with correlation coefficients $r = 0.476$, $P < 0.001$, and $r = 0.534$, $P < 0.001$, respectively (Fig. 3). The MCR of hTSH of all patients was also related to the serum TT_3 concentration with a correlation coefficient $r = 0.537$, $P < 0.001$. Likewise the MCR was related to the endogenous creatinine clearance with a correlation coefficient $r = 0.609$, $P < 0.001$ (Fig. 4). None of the patients had overt renal disease, and all had normal serum creatinine concentrations.

Endogenous hTSH serum concentrations and PR. The serum concentrations and PR of hTSH are listed in Table II. In control patients the PR was 104.3±41.4 mU/day or 55.2±21.0 mU/day per m². In hypothyroid

TABLE II
hTSH Serum Concentrations, MCR Rate and PR in Various Thyroid and Endocrine Disorders

Clinical state	No. of patients	Sex F/M	TT₄*	Free T₄	TT₃*	hTSH	hTSH‡ MCR	hTSH PR
			μg/100 ml	*ng/100 ml*	*ng/100 ml*	*μU/ml ±SD*	*ml/min ±SD*	*mU/d ±SD*
Controls	16	6/10	6.5	1.3	171	1.45±0.55	50.7±15.6	104.3±41.4
Primary hypothyroidism	12	12/0	2.0	0.3	68	105.3±85.8	30.9±8.3§	4,440±3,732
Before treatment	5	5/0	2.9	0.4	80	106.0±86.2	33.1±9.0	4,244±1,414
After treatment	5‖	5/0	2.2	0.3	112	63.2±58.8	33.7±11.0	2,461±1,457
Hyperthyroidism	6	4/2	15.3	4.2	595	<0.5	60.9±4.9§	<43.9±3.5
Decreased thyroid reserve¶	6	4/2	5.1	0.9	153	17.1±12.2	40.9±7.3**	956±622
Hyperfunctioning thyroid nodule	4	2/2	7.3	1.5	207	<0.5	53.8±19.9**	<38.7±14.0
Empty sella syndrome	4	2/2	6.3	1.4	195	1.80±0.90	46.6±8.2**	118.5±51.0
Miscellaneous‡‡	7	2/5	8.3	1.6	222		42.2±7.9**	

* TT₄ (normal 4–11 μg/100 ml) and TT₃ (normal 150–250 ng/100 ml) done by competitive-protein-binding assay at Boston Medical Laboratory, Waltham, Mass. (5).
‡ See footnote to Table I.
§ Significantly different from controls ($P < 0.05$).
‖ Five hypothyroid patients given triiodothyronine 50 μg/day intravenously for 10 days.
¶ See Table III for a detailed description of these six patients.
** Not significantly different from controls ($P > 0.10$).
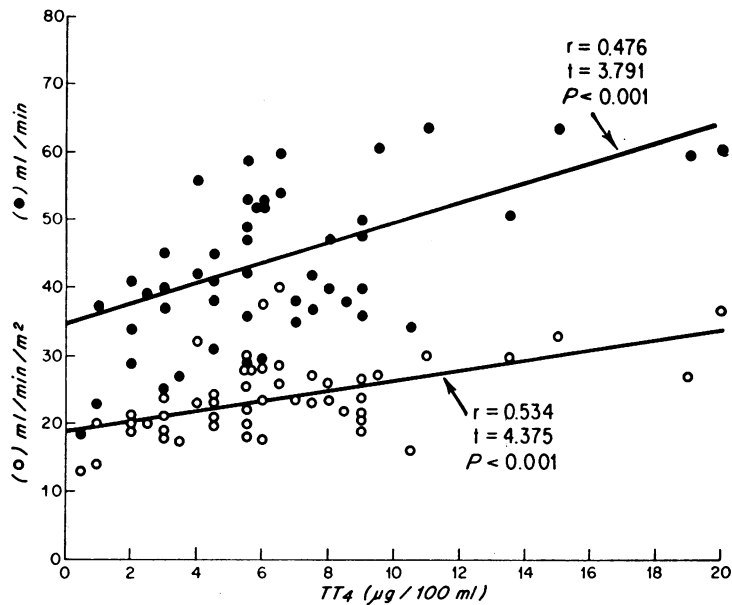‡‡ See text for a description of these seven patients.

FIGURE 3 Correlation of serum total thyroxine with MCR (●) and MCR/m² (○) of hTSH. The regression line was calculated by the method of least squares.

patients the PR was 4440±3732 mU/day or 2767±2278 mU/day per m² ($P < 0.001$), while in hyperthyroid patients the PR was undetectable ($< 43.9±3.5$, $P < 0.005$). The PR was also undetectable in patients with single hyperfunctioning thyroid nodules. In the patients with the empty sella syndrome, the PR was in the normal range at 119±51 mU/day or 63±28 mU/day per m².

The patients with decreased thyroid reserve require detailed comment and specific characterization. The clinical data of these six patients are presented in Table III. There were two men (ages 41 and 65) and four women (ages 46–60). The serum TT₄ ranged from 4.0 to 6.0 μg/100 ml, the free T₄ varied from 0.8 to 1.1 ng/100 ml, the TT₃ ranged from 120 to 195 ng/100 ml, the RaI uptake ranged from 14 to 20%, and the basal metabolic rate varied from − 19 to + 10%. The T₃R was low–normal in all, suggesting no abnormality in the serum thyroxine-binding proteins. The basal serum hTSH was elevated in each patient and ranged from 6.2 to 41.0 μU/ml, with five of the six patients having serum hTSH concentrations of 16.5 μU/ml or less. Five of the six had a blunted rise in the RaI uptake and TT₄ after bTSH administration for 3 days. The hTSH response to the intravenous administration of a single bolus of 200 μg of TRH (5) was abnormal with peak concentrations of hTSH varying from 44 to 150 μU/ml. In all of these patients, the mean PR was approximately nine times normal at 956±622 mU/d or 544±342 mU/day per m².

In patients with either decreased thyroid reserve

or primary hypothyroidism, the elevated serum hTSH concentration was found to be related to an increased hTSH PR with a correlation coefficient $r = 0.93$, $P < 0.001$ (Fig. 5).

Effect of acute thyroid hormone replacement. Acute triiodothyronine therapy (50 μg intravenously for 10 days) in five hypothyroid patients produced no signifi-
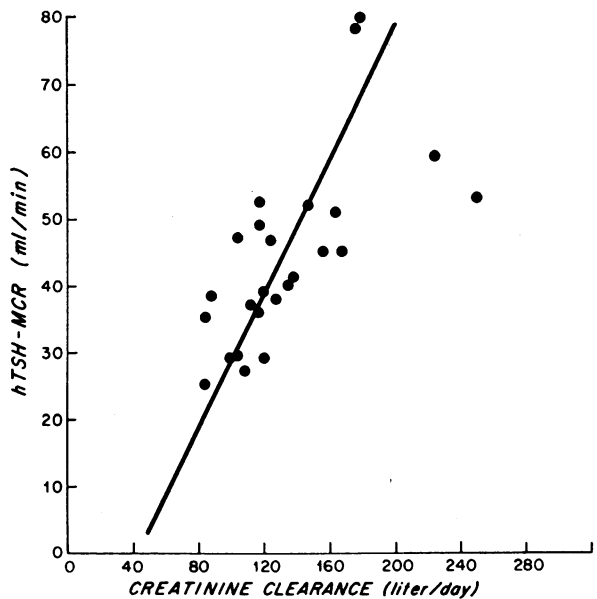

FIGURE 4 Correlation of endogenous creatinine clearance with hTSH MCR. The regression line was calculated by the method of least squares. $P < 0.001$, $r = 0.609$, $t = 4.167$.

TABLE III

Laboratory Data in Six Patients

Patient	Age	Sex	Diagnosis	TT₄*	Free T₄	TT₃*	RAI uptake
	yr			$\mu g/100\ ml$	$ng/100\ ml$	$ng/100\ ml$	$\%$
H. L.	65	M	Hashimoto's thyroiditis	4.0	1.0	195	20
R. M.	41	M	Graves' disease treated ¹³¹I	4.5	0.8	120	16
M. F.	46	F	Hashimoto's thyroiditis	6.0	1.0	165	19
E. D.	60	F	Graves' disease treated ¹³¹I	4.5	0.8	170	20
L. K.	58	F	Euthyroid Graves' disease§	6.0	1.1	150	18
J. R.	56	F	Graves' disease treated ¹³¹I	5.5	0.9	120	14

* TT_4 (normal 4–11 $\mu g/100$ ml) and TT_3 (normal 150–250 ng/100 ml) done by competitive-protein-binding assay at Boston Medical Laboratory, Waltham, Mass. (5).

‡ See footnote to Table 1.

§ Patient presented originally (1969) with normal T_4, free T_4, TT_3, and normal RAI uptake that was nonsuppressible with cytomel. She was followed for 3 y without therapy and at this point her RAI uptake was normally suppressible (22) and the above studies were determined.

cant change in the MCR (33.1 to 33.7 ml/min), whereas this therapy significantly decreased the serum concentrations (from 106 to 63 $\mu U/ml$) and PR (from 4,244 to 2,461 mU/day) of hTSH.

DISCUSSION

The present study has utilized the constant infusion to equilibrium method of Tait (9) to determine the MCR and calculate the PR of hTSH in man. Previous determinations of hTSH MCR in man were performed by a single injection method (7, 8) involving the following assumptions: (a) the labeled hormone is instantly distributed through its volume of distribution; (b) labeled hormone is distributed through a single compartment; (c) a steady state existed during the study period whereby clearance of hTSH remained constant; and (d) labeled and unlabeled hTSH are metabolized at an identical rate. However, other studies have shown that hTSH (7) is distributed through a compartment larger than the plasma volume and complete metabolism occurs in a multiexponential fashion, raising a question as to the validity of the single injection method for estimation of hTSH MCR. The present study does not assume instantaneous mixing nor any number of compartments for the volume of distribution for labeled hTSH. The constant infusion to equilibrium method does assume (a) that a steady state or equilibrium had been achieved, and (b) that labeled and unlabeled hormone had similar rates of metabolism. Although absolute equilibrium cannot be proved unequivocally, no significant variation in the levels of immunoprecipitable [¹³¹I]hTSH were observed after 3 h of constant infusion. This observation

agrees with similar studies performed for other labeled pituitary glycoproteins where apparent equilibrium was achieved after 3 h (11, 12). That ¹³¹I-labeled and unlabeled hTSH have similar rates of metabolism was first observed by Odell et al. (7) and has been confirmed by our recent demonstration that labeled and unlabeled hTSH disappeared from canine plasma with identical curves.[2]

The MCR of hTSH in control patients observed in this study of 50.7 ml/min was similar to that found by Odell et al. of 42.5 ml/min (7) and Beckers et al. of 56.2 ml/min (8). The small difference between the MCR observed in control patients in the present study and that of Odell et al. (7) may be related to the fact that the present study included 10 of 16 men, whereas the latter had 8 of 12 women. This apparent sex difference has been shown to be related to surface area in the present study and can be resolved by correcting the MCR for surface area. Hypothyroid patients had significantly reduced MCR of hTSH (30.9 ml/min) which agrees with the data (36.3 ml/min) of Odell et al. (7) but differs from that of Beckers et al. (8) who showed no significant difference between normals (56.2 ml/min) and hypothyroid (62.8 ml/min) patients. Contrariwise, hyperthyroid patients had accelerated MCR (60.9 ml/min), which agrees with the observations (60.6 ml/min of Beckers et al. (8). These findings suggested that the MCR of hTSH was related to the metabolic state of the patient, and a significant ($P < 0.001$) correlation was found between the serum

[2] Ridgway, E. C., F. R. Singer, B. D. Weintraub, and F. Maloof. Metabolism of human thyrotropin in the dog. Submitted to *Endocrinology* for publication.

		bTSH Stimulation						
		RAI uptake		TT$_4$			hTSH‡	hTSH
BMR	Thyroid antibodies	Before	After	Before	After	hTSH	MCR	PR
%		%		µg/100 ml		µU/ml	ml/min	mU/day
+10	Strongly positive	N.D.	N.D.	N.D.	N.D.	12	43.6	753
−8	Negative	16	20	6.0	6.0	12.5	39.5	711
−9	Strongly positive	19	27	6.0	6.0	6.2	52.3	467
+2	Negative	20	10	4.5	5.0	14.5	42.6	889
−19	Strongly positive	18	15	6.0	5.5	16.5	30.4	722
N.D.	Negative	14	27	5.5	5.5	41	37.2	2,196

TT$_4$ and triiodothyronine concentration and the MCR hTSH. Previous workers had also shown that the clearance rate of TSH injected into animals was dependent on the metabolic state of the animal but unrelated to the presence of thyroid tissue per se (13, 14).

The exact sites of clearance of hTSH have not been resolved. We have recently studied the clearance of [^{131}I]hTSH in the dog and shown that significant clearance occurred only in the kidney and not in the liver, thyroid, or femoral muscle.[2] These data are supported by the present study, which demonstrated a significant ($P < 0.001$) correlation between the endogenous creatinine clearance and MCR of hTSH, and agree with the observation that patients with renal insufficiency had reduced MCR of hTSH (8). Whether clearance by the kidney involves degradation or excretion is unknown. Previous studies (15, 16) have shown bioassayable thyroid-stimulating substances in the urine of myxedematous and some normal subjects suggesting that hTSH, like other glycoproteins, is partially excreted into the urine in a biologically active form.

The calculation of the hTSH PR from the observed hTSH MCR depends on an accurate measurement of the serum concentration of endogenous hTSH and the assumption that the endogenous hTSH concentration remains constant for the 24-h period. Accurate determinations of endogenous hTSH have been possible in primary hypothyroidism, but precise distinctions between normal and hyperthyroid patients have only recently been reported (4, 5). These newer methods have utilized nonequilibrium conditions, highly purified labeled hTSH, higher dilutions of sera, and incubation of standards in "TSH-free" serum. These methods

permit differentiation of hTSH concentrations in normal and hyperthyroid patients and yield lower values for normal serum hTSH than had previously (7, 8) been used for calculation of the hTSH PR. Further, the assumption that the 24 h production rate of hTSH remains constant has been supported by studies showing constant blood levels of hTSH during the 24-h period (3, 17, 18). However, more recent studies (19, 20) utilizing sensitive radioimmunoassays have demonstrated a significant small and brief rise in hTSH concentra-
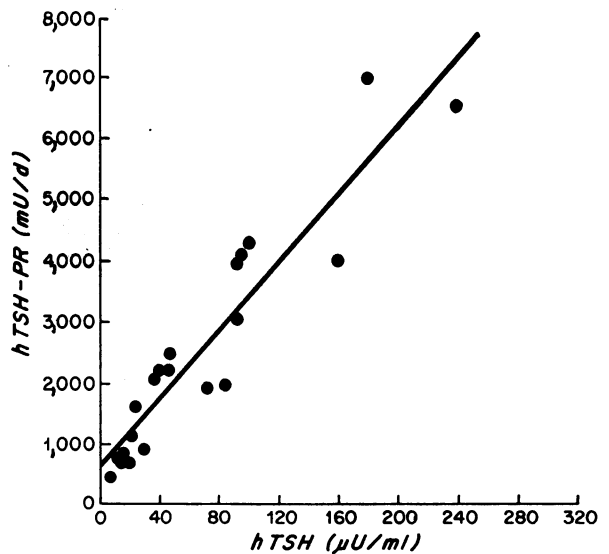

FIGURE 5 Correlation of serum hTSH concentration and hTSH PR. The regression line was calculated by the method of least squares. $r = 0.93$.

tion in the early morning hours, suggesting a circadian variation in TSH production. Thus the results in the present study, which assumes constant production of hTSH, may be slightly low since this method does not include the brief rise of hTSH during the early morning hours.

The mean calculated hTSH PR for control subjects observed in the present study was lower than that reported by Odell et al. (7) or Beckers et al. (8). Since the hTSH MCR in these three studies were similar, the disparity in hTSH PR was due to the higher endogenous serum hTSH concentrations found in the control patients of the previous investigators. Odell et al. (7) used a radioimmunoassay in which serum was first concentrated in order to detect normal levels, whereas Beckers et al. (8) were not able to distinguish normal from hyperthyroid hTSH serum concentrations. The data of the latter investigators (8) suggested that the hTSH PR in hyperthyroidism was slightly higher than that in normal patients. The present study clearly demonstrated that hyperthyroid patients have hTSH PR that are lower than normal patients. Further, patients with hyperfunctioning thyroid nodules had undetectable hTSH PR that could not be distinguished from classical hyperthyroid patients. Nevertheless, further refinement of the hTSH assay may detect subtle differences in the hTSH serum concentrations and PR in these two disorders similar to that found for ACTH production in the single adrenal adenoma versus adrenal hyperplasia in Cushing's disease (21).

Patients with primary hypothyroidism or decreased thyroid reserve had elevated serum concentrations and production rates of hTSH. Although a small part of the elevated serum hTSH concentrations in these two disorders was related to delayed clearance, the major determinant was an accelerated PR. For the first time, this study has demonstrated that an elevated serum hTSH level was related to an elevated PR of hTSH throughout the spectrum of primary thyroidal failure. Furthermore, acute treatment of five hypothyroid patients with intravenous triiodothyronine for 10 days decreased the hTSH PR and serum concentrations before significant changes were observed in the hTSH MCR, suggesting that the acute changes in serum TSH concentrations resulted from central pituitary inhibition before peripheral clearance of hTSH was altered.

The patients with decreased thyroid reserve had elevated serum concentrations and PR of hTSH, clearly demonstrating that although such patients appear clinically euthyroid, their pituitary glands are secreting more hTSH than normal. Thus, these patients were probably secreting less thyroid hormone than was normal for their individual metabolic requirements, and

the increase in pituitary hTSH secretion may be an early and very sensitive indicator of subtle primary thyroid failure. The importance of slight but significantly elevated serum hTSH concentrations requires thorough investigation, since the consequence of this subclinical metabolic state on the growth and function of the pituitary and on hTSH and other pituitary hormones may have important implications.

In conclusion, these studies on patients with a variety of thyroid disorders showed that the primary determinant of the serum hTSH concentration is the pituitary hTSH secretion rate rather than its MCR. Although a highly significant relationship exists between the hTSH clearance rate and the serum concentration of thyroxine and triiodothyronine, the changes in the hTSH clearance rate in various thyroid disorders are less than and may occur later than changes in the hTSH secretion rate.

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