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Kinetic analysis of thyroxine outside thyroid with 131-I-tyroxine by aid of computer–with special reference to liver diseases

Yasuhiro Yumoto* Tsunko Namba†

Hideo Yamamoto‡

*Okayama University,

†Okayama University,

‡Okayama University,

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Yasuhiro Yumoto, Tsunko Namba, and Hideo Yamamoto

Abstract

By auming a three-compartment model, kinetic analysis of peripheral hyroxine distributions in various organs was represented by the alues calculated on the basis of the disappearance curve of 131I-T4 radioactivity in the serum, time dependent curve of radioactivity over the liver and urinary excretion of 131I-T4 in attempts to clarify the kinetic distribution of the thyroxine and the time dependent pool size of thyroxine in each compartment such as serum pool, liver pool, and the other pool, As a result it has been demonstrated that pool size3 of tyroxine, in the serum, liver and the other pool are enlarged in hyperthyroidism, while they are decreased in hypothyroidism in respective pools. We have recognized the reduction in the values of the liver pool size of 131I-thyroxine and 131I-thyroxine excretion into the bile, while the increase of 131I-thyroxine excretion into the urine in the cases of chronic hepatitis and cirrhosis of the liver, but the thyroxine concentration in the serum to remain within the normal level in liver diseases. As a result of the reduction in the liver pool size of 131I-thyroxine and in its uptake into the liver, the other pool size enlarges to compensate the reduction and the function of the other pool is elevated.

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KINETIC ANALYSIS OF THYROXINE OUTSIDE THYROID WITH ^{131}I-THYROXINE BY AID OF COMPUTER—WITH SPECIAL REFERENCE TO LIVER DISEASES

Yasuhiro YUMOTO, Tsunko NAMBA and Hideo YAMAMOTO*

Department of Internal Medicine, Okayama University Medical School, Okayama, Japan (Director: Prof. K. Kosaka)

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As reported by many authors (1-6) the liver plays an important role in the peripheral metabolism of thyroxine in man. LEMON, ENGBRING and ENGSTROM (4) measured the rate of radioactivity disappearance in the blood of patients with liver diseases during initial 50 minutes of intravenous injection of ^{131}I-L-thyroxine ($^{131}IT_4$) and found that the rate of decline in the level of tracer was abnormally slow in hypothyroidism and abnormally rapid in hyperthyroidism. CAVALIERI *et al.* (1) and HADDAD (2) established a two-compartment model for liver diseases representing the intravascular and the extravascular tissue pools of thyroxine, and analyzed the plasma disappearance curves. As a result they found a decrease in the hepatic thyroxine space and pool size. BLOMSTEDT and PLANTIN (7), using only the time dependent curves of plasma disappearance rate of tracer, proposed a four-compartment system for the analysis of the distribution and metabolism of labeled thyroxine in normal humans, but their four-compartment system corresponds essentially to the two-compartment system analysis.

In our study we set up a three-compartment system using plasma disappearance curves, time dependent counting over the liver, and the tracer excretion to the urine, to analyze the metabolism of the labeled thyroxine, and compared differences in the peripheral metabolism of thyroxine in normal individuals as well as in patients with various thyroid diseases and liver diseases. The results are presented in this report.

MATERIALS AND METHODS

In vitro studies: Before injection of tracer, 20 ml each of various bloods was collected for the determination of PBI, free T_4, serum T_4 concentration, using tetrasorb kit (Dinabot Lab.) and serum TBG capacity.

In vivo studies: Further, other 10 ml each was transferred to a sterile vial containing citrate. To this citrated blood was added about 60.0 μCi of ^{131}I-T_4 (less

* School of Enginneering, Okayama University, Okayama, Japan

than 2 μg of T_4), and exactly 8 ml of the blood containing tracer was injected during a period of 10 sec into anticubital vein. The remaining 2 ml was used as a counting standard. Samples (2.5 ml) of blood were withdrawn at intervals of 5 or 10 minutes, from 10 to 90 minutes after injection of the tracer. Subsequent samples of blood were collected by vein puncture at 2, 4, ··· and 6 hours, and thereafter at 24-hour interval for 10 to 14 days.

The samples were immediately transferred to tubes containing citrate, plasma was separated by centrifugation and its radioactivity was assayed. Collections of total urine were made during the initial 6 hours and from 6 to 24 hours after injection. Total ^{131}I counts in the urine were taken. All the subjects were given 200 mg of KI per day per oral throughout the study in order to minimize thyroidal uptake of ^{131}I.

Method of external counting over the liver: Monitoring of radioactivity in the region of the liver was done with a 2×2 inch scintillation detector fitted with a flat field lead collimater. The face of the collimator was placed in contact with the subject at a point of the mid-clavicular line and 3 minutes after injection of the tracer adjustments were made in the detector in order to obtain a maximal counting rate. The skin was marked to permit accurate placement for subsequent counts.

The subjects comprised 11 cases of various liver diseases including 3 cases of chronic hepatitis, 3 of liver cirrhosis, one of fatty liver, one of hemochromatosis, one of BUDD-CHIARI's syndrome and 2 cases of hyperthyroidisms, one of hypothyroidisms and 3 of normal subjects as illustrated in Table 1.

TABLE 1 RESULTS OF ^{131}I THYROXINE

Cases	Sex	Age years old	Diagnosis	weight kg	Tetrasorb $\mu g T_4$/dl serum	PBI μg/dl	Plasma volume l	T_4 excretion into urine %
H.H.	M	21	Normal	62	9.2	3.7	2.72	11.2
T.S.	M	22	Normal	58	9.45	3.9	2.50	10.3
S.N.	M	25	Hyperthyroidism	68	25.45	11.99	2.72	17.7
R.U.	F	17	Hyperthyroidism	41.5	33.71		2.50	11.7
T.S.	F	39	Hypothyroidism	58	2.90	6.46	1.89	9.6
R.Y.	M	41	Chr. Hepatitis	57	11.60	5.60	2.38	12.1
S.A.	F	53	〃	52	4.80	6.53	2.10	12.3
A.K.	M	34	〃	54.5	8.20	7.7	2.10	11.6
A.D.	F	58	Liver Cirrhosis	54.5	9.62	6.1	2.00	14.7
Y.O.	M	58	〃	62	8.60	6.3	1.85	11.5
S.U.	M	28	〃	55.5	8.90	6.8	2.01	12.6
S.M.	M	42	Fatty Liver	56	7.32	8.4	1.85	14.2
S.T.	F	50	Hemochromatosis	47	11.92	5.15	2.38	12.9
K.K.	F	47	Budd chiaris symdrom	46		4.7	1.88	16.3

$$P_1=\int_0^{1440} Q_1(t)dt, \quad P_2=\int_0^{1440} Q_2(t)dt, \quad P_3=\int_0^{1440} Q_3(t)dt, \quad U=k_{01}P_1, \quad B=k_{02}P_2$$

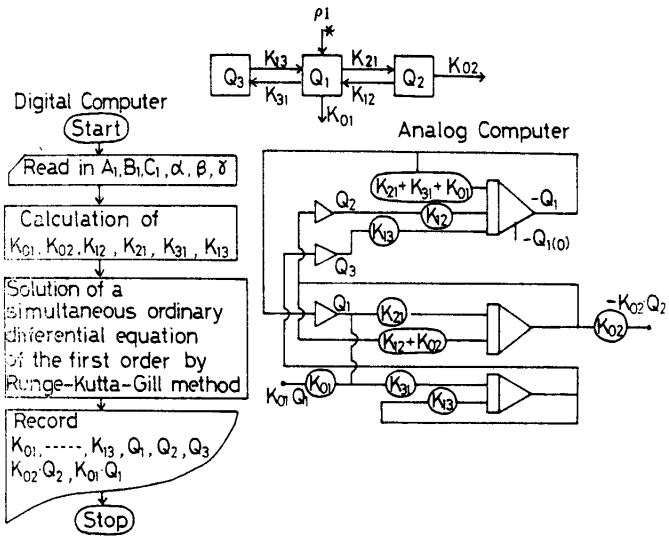

Fig. 1 Models of distribution of the thyroxine in the 3-compartment system and the digital and analog computer programs.
Compartment Q_1 represents plasma; compartment Q_2, the extravascular space of the liver; and compartment Q_3, all nonhepatic tissues. Tracer (*) enters the system via compartment Q_1 at a rate ρ_1. Fractional rate constants (k) for distribution and metabolism are indicated adjacent to the appropriate arrows.

TURNOVER STUDY AND *in vivo* TESTS.

Fractional rate constant					Pool size ($Q_{1(0)}=1.0$)				
k_{01} ×10-4/min	k_{02} ×10-4/min	k_{12} ×10-3/min	k_{13} ×10-2/min	k_{21} ×10-2/min	P_1	P_2	P_3	U	B
1.18	3.08	6.716	4.087	1.338	419.24	803.74	54.83	0.0450	0.2267
0.96	3.22	6.791	6.115	1.379	380.01	749.99	57.34	0.0402	0.2415
2.42	4.78	4.391	2.513	1.026	339.9	638.39	167.89	0.0823	0.3051
2.964	1.144	8.157	13.343	1.516	434.3	779.3	28.32	0.1287	0.0892
2.534	2.844	3.944	1.875	0.718	437.01	654.91	135.95	0.1107	0.1837
2.49	5.16	8.35	16.137	0.991	487.54	511.85	144.85	0.1214	0.2642
					571.21	493.4	36.72	0.1234	0.1938
2.16	3.927	5.879	7.272	0.595					
3.11	2.74	4.961	6.172	0.693	501.4	593.8	186.51	0.1559	0.1627
3.63	4.905	8.407	4.088	0.367	732.7	284.83	108.35	0.266	0.1397
3.10	6.0	4.237	3.986	0.530	479.37	468.76	157.10	0.1486	0.2819
2.476	3.73	6.203	11.503	0.616	576.6	489.60	117.99	0.1428	0.1828
1.328	1.83	3.749	4.863	1.314	817.11	174.09	134.70	0.1085	0.3186
3.43	2.11	4.024	3.547	0.449	542.70	482.3	216.30	0.1801	0.1018

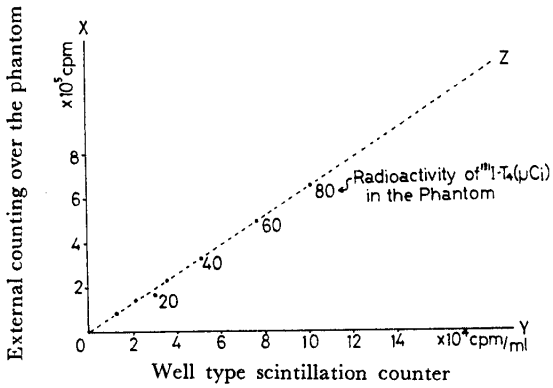

Fig. 2 The abscissa shows values of the radioactivity of $^{131}IT_4$ obtained by use of two inches scintillation detector with the straight collimater over the liver phantom, and the ordinate shows the values of radioactivity of radioactive content (1ml) in the liver phantom.

The number on the correlation line (Z) represents the values of total radioactivity of ^{131}I-T_4 in the liver phantom.

Analysis of the data: After intravenous injection of $^{131}IT_4$ about 50μ Ci, the disappearance curves of radioactivity in the serum were obtained and the curves were replaced by three exponential functions obtained by graphic method with the least square method. Plasma disappearance curve $Q_1(t)$ is given as the function of the following formula. (Fig. 3)

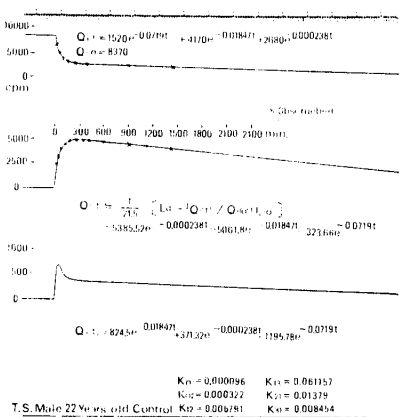

Fig. 3 Distribution curves of ^{131}I-thyroxine in 3-compartment pools according to the three compartment model of Fig. 2 by analog computer.

$$Q_1(t) = A_1e^{-\alpha t} + B_1e^{-\beta t} + C_1e^{-\gamma t} \quad \cdots\cdots\cdots\cdots\cdots\cdots (1)$$

Here the relation of $\alpha > \beta > \gamma$ is established. The external counting over the liver is taken and the following curve $L(t)$ composed of various components is obtained:

$$L(t)=[Q_2(t)V_L+Q_1(t)V_P]\times D\cdot E \quad \cdots\cdots (2)$$

Here is the counting rate observed in counts per min. recorded by the hepatic detector at time t. Supposing $Q_2(t)$ is to be the concentration of tracer in the extravascular space of the liver, at time t. V_L is a virtual mass of liver within the collected field of the detector. V_P is the virtual volume of plasma, in liters within the collimated field, D is the injected dose in microcuries, and E is the overall detection efficiency in counts, per minute per microcurie, which is assumed to be identical with label in the liver and plasma within the collimated field.

$$L(0)=Q_1(0)V_PDE \quad \cdots\cdots (3)$$

When we substitute formula (2) for (3), the following formula is obtained :

$$Q_2(t)V_LDE=L(t)-(Q_1(t)/Q_1(0)L(0)$$

Then we set up 3 compartment model (Fig. 1) upon which differential equation is formulated.

$$\begin{aligned} dQ_1(t)/dt &= k_{12}Q_2(t)+k_{13}Q_3(t)-(k_{21}+k_{31}+k_{01})Q_1(t)+\rho_1\vartheta(t) \\ dQ_2(t)/dt &= k_{21}Q(t)-(k_{12}+k_{02})Q_2(t) \\ dQ_3(t)/dt &= k_{31}Q_1(t)-k_{13}Q_3(t) \end{aligned} \quad \cdots\cdots (4)$$

We know that an ordinary differential equation with constant coefficients has as its solution a linear combination of exponentials. The solution thus turns out to be the equation of the form (5).

$$Q_t(t)=Aie^{-\alpha t}+Bie^{-\beta t}+Cie^{-\gamma t} \quad \cdots\cdots (5)$$

Urinary excretion of radioisotopes during 24 hours is computed by the next formula.

$$U(t)=k_{01}\int Q_1(t)dt \quad \cdots\cdots (6)$$

Taking formula (4) for Laplace transformation, and applying Cremer's formula and the method of undetermined coefficiency, the following can be obtained (see appendix).

$$\alpha+\beta+\gamma=k_{11}+k_{22}+k_{13}$$
$$\alpha\cdot\beta\cdot\gamma=k_{11}k_{22}k_{13}-k_{13}\cdot k_{31}\cdot k_{22}-k_{12}\cdot k_{21}\cdot k_{13}$$
$$\alpha\beta+\beta\gamma+\gamma\alpha=k_{11}\cdot k_{22}+k_{22}\cdot k_{13}+k_{13}k_{11}-k_{13}\cdot k_{31}-k_{12}\cdot k_{21}$$
$$A_1(\beta+\gamma)+B_1(\alpha+\gamma)+C_1(\alpha+\beta)=(k_{22}+k_{13})(A_1+B_1+C_1)$$
$$k_{11}=k_{31}+k_{21}+k_{01},\quad k_{22}=k_{12}+k_{02},\quad k_{33}=k_{13}$$
$$A_1\beta\gamma+B_1\alpha\gamma+C_1\alpha\beta=k_{22}\cdot k_{33}(A_1+B_1+C_1)$$

In calculation of the rate constant of k_{01}, k_{02}, k_{12}, k_{21}, k_{13}, k_{31} are made by A_1, B_1, C_1, α, β, γ which are taken from the disappearance curves of blood and the values of urinary excretion of radioisotopes, we substitute each rate constant for that of formula (4) and calculate the ordinary differential equation by the method of RUNGE-KUTTA-GILL, using digital computer Facom 270—20. After values of $k_{01}-k_{31}$ are obtained on the basis of given data, the time dependent curves of $Q_1(t)$, $Q_2(t)$ and $Q_3(t)$ are normalized respectively under the following conditions of

$Q_1(0)=1.0 \quad A_1+B_1+C_1=1 \quad Q_2(0)=0.0$

Moreover, values of each pool size (Pi), urinary excretion (U) and biliary excretion (B) during 24 hours are calculated under the conditions that we have expressed in terms of

$$P_i=\int_0^{1440} Q_i(t)dt, \qquad U=k_{01}\int_0^{1440} Q_1(t)dt, \qquad B=k_{02}\int_0^{1440} Q_2(t)dt$$

We represent the value of T_4 in serum by $Q_1(0)$ which are obtained by multiplying plasma volume by T_4(ug) in 1ml of the serum by means of tetrasorb kit.

RESULTS

In vitro studies:

Table 1 presents the pertinent data for each of the control subjects and various thyroid and liver diseases.

Among the controls the concentration of serum T_4 using tetrasorb kit was $9.923\pm1.87\,\mu g/dl$. The normal range by this method was 8 to 11.0 $\mu g/dl$. The concentration of serum T_4 was $9.08\pm3.24\,\mu g/dl$ in chronic hepatitis, $9.25\pm2.01\,\mu g/dl$ in liver cirrhosis, $25.75\pm5.69\,\mu g/dl$ in hyperthyroidism and $2.33\pm0.32\,\mu g/dl$ in hypothyroidism. The concentration of PBI was $6.92\pm1.00\,\mu g/dl$ in chronic hepatitis, $5.96\pm1.43\,\mu g/dl$ in liver cirrhosis. In liver diseases the concentration of serum T_4 was determined on day 2 and 7 of the kinetics day and the average value of the serum T_4 concentration was taken. Thyroxine binding capacity of serum TBG was slightly decreased in liver cirrhosis, in the control the TBG capacity ranged from 11 to 23 μg T_4 iodine per 100 ml (mean 17). The concentration of free T_4 in the controls varied from 0.87 to 3.28 mμg T_4 iodine per 100 ml. The values obtained in liver diseases were within normal range.

In vivo studies: The disappearance of tracer from plasma and the rise in hepatic radioactivity were slower during 100 min. in liver diseases. Table 1 shows the individual values for the fractional rate constant of each pool and each pool size for 24 hours after injection in various liver diseases and thyroid disorders. If we normalize $Qi(t)$ with the following condition, $Q_1(0)=1$, $A_1+B_1+C_1=1$, $Q_2(0)=Q_3(0)=0$ time dependent $Qi(t)$ can be represented as in Figs. 4, 5, 6.

Time dependent curves of $Q_1(t)$ which represent the disappearance curve of ^{131}I-T_4 from the plasma being decreased more slowly in the early stage in chronic hepatitis and liver cirrhosis than in normal subjects which are represented by a straight line in Fig. 4. The time dependent curves of $Q_2(t)$, showing the time dependent change of T_4 pool in the liver, rise

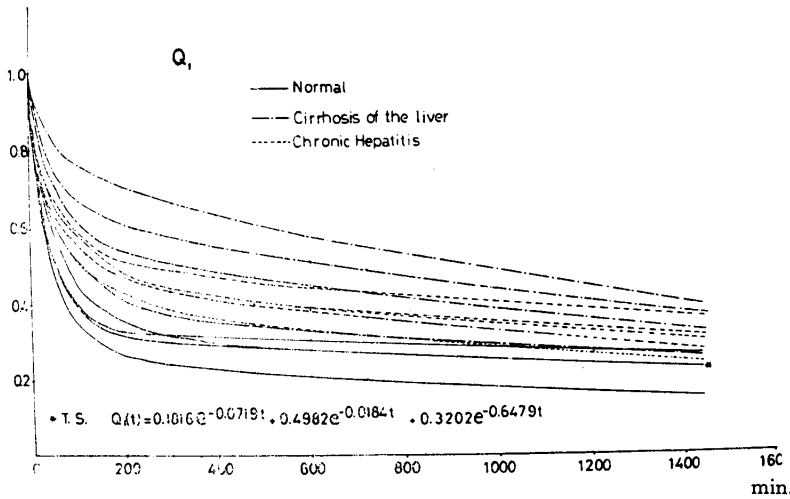

Fig. 4 Distribution curves of $^{131}IT_4$ in Q_1 pool in various liver diseases.

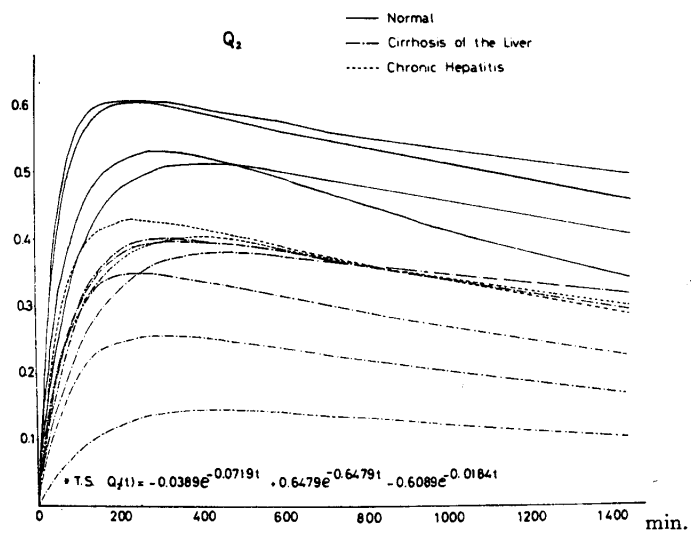

Fig. 5 Distribution curves of $^{131}IT_4$ in Q_2 pool in various liver diseases.

more slowly in the cases of chronic hepatitis and liver cirrhosis than those in normal subjects during the initial 60 min. The time showing the maximum point of the time dependent curve of $Q_2(t)$ is prolonged in the cases of liver cirrhosis and also the maximum is decreased more in liver diseases (Fig. 5). These facts indicate that the T_4 uptake into the liver is decreased in liver diseases, while the maximum point of time dependent curve of $Q_2(t)$ decreases more markedly in liver cirrhosis and chronic liver diseases

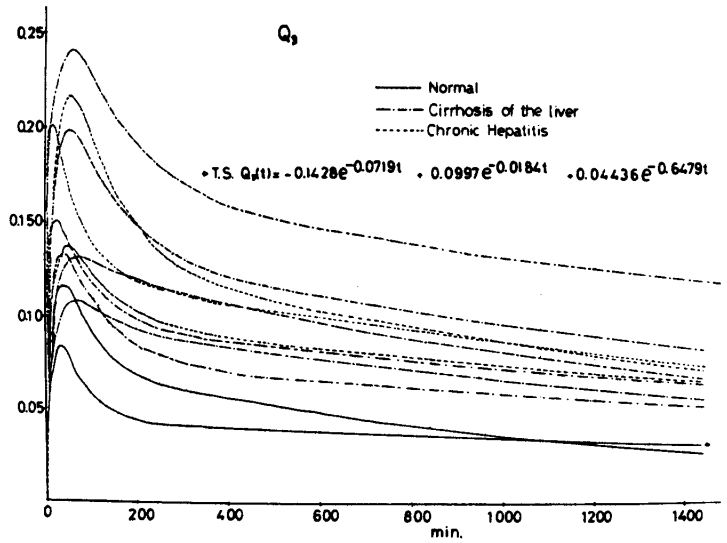

Fig. 6 Distribution curves of the $^{131}IT_4$ in Q_3 pool in various liver diseases after intravenous administration.

(Fig. 5). The time dependent curves of $Qi(t)$ of the cases of hyperthyroidism and hypothyroidism with normal liver function, reveal no significant difference from those of normal subjects represented in a straight line (Fig. 5). If $Qi(t)$ is integrated from 0 to 1440 min. and the blood pool, liver pool, the other pool, the amount of T_4 excreated into the urine and that of bile can be expressed as P_1, P_2, P_3, U, B respectively, it becomes as follows:

$$P_1=\int_0^{1440} Q_1(t)dt \qquad P_2=\int_0^{1440} Q_2(t)dt \qquad P_3=\int_0^{1440} Q_3(t)dt \qquad U=k_{01}P_1$$
$$B=k_{02}P_2$$

These individual values are indicated in Table 1 according to various diseases. Here the $Q_1(0)$ is replaced by the total value of T_4 in serum, expressed in terms of P'_1, P'_2, P'_3, U', B', which show the respective values in the lower space of Table 2. In the cases of hypothyroidism the plasma T_4 pool (expressed by P'_1), hepatic pool (P'_2) and the other pool (P'_3), are elevated nearly twice or about 3 times the normal means, while in the cases of hypothyroidism P'_1, P'_2, P'_3 and excretion values of T_4 into urine and bile are decreased one-third or less the normal means as anticipated. It is noteworthy that in chronic hepatitis and liver cirrhosis, the hepatic pool size (P'_2) is decreased, whereas the other pool size (P'_3) is incremented. However, the T_4 iodine concentration in the serum is within

TABLE 2 RESULTS OF TURNOVER STUDY OF THYROXINE ACCORDING TO 3 COMPARTMENT MODEL, P_1, P_1'; P_2, P_2', P_3, P_3'; U, U' AND B, B'.

	P_1 (24 hr)	P_2 (24 hr)	P_3 (24 hr)	Urine (24 hr)	Bile (24 hr)
Normal (3 cases)	406.98	776.87	56.09	0.0481	0.2341
Hyperthyroidism (1 case)	339.90	638.39	167.89	0.0823	0.3051
Hypothyroidism (1 case)	437.01	645.91	135.95	0.1170	0.1837
Chronic Hepatitis (3 cases)	549.33	499.12	134.13	0.1061	0.2351
Liver Cirrhosis (5 cases)	605.24±137.96	415.73±154.95	153.49±41.71	0.1669±0.0537	0.1979±0.0845

	T_4 (μg/dl)	PV (l)	P_1' (mg/day)	P_2' (mg/day)	P_3' (mg/day)	Urine' (μg/day)	Bile' (μg/day)
Normal	10.9	2.55	113.3	216.3	15.62	13.4	65.2
Hyper.	25.75	2.38	208.3	391.2	102.89	50.4	186.9
Hypo.	2.33	1.89	32.5	28.4	5.98	5.1	8.08
Chr. Hep.	10.09	2.15	119.2	108.3↓	29.09↓	23.0↓	50.9↓
L. C.	10.25	2.06	127.8	87.7↓	32.38↓	35.2↓	41.9↓

the normal range.

The individual values for the fractional rate constant for distribution and metabolism are expressed as $k_{01}, \cdots k_{31}$ which are represented in Fig. 1. In controls, the calculated rate constant of k_{21}, expressing the uptake from the plasma to liver, is 0.0135 min^{-1}, k_{12} 0.00675 min^{-1} and k_{02} 0.000315 min^{-1} in average. The cases of chronic hepatitis and liver cirrhosis showed a more remarkable decrease in the values of k_{02} and k_{21} than normal controls, which showed a slight increase in the value of k_{01}. Control subjects excreted 4.89 % administered dose (range 3.0 to 6.5 %) into the urine in avarage during the initial 6 hours of the study. The cumulative urinary excretion during the period of 0 to 24 hours averaged 13.4 μg T_4. The cases of liver diseases with diminished P'_2 showedrema rkably decreased values of T_4, while they gave increased values of T_4 excreted into the urine. In this instance, the integrated values of T_4 (μg) excreted into the urine and bile averaged 78.6 μg T_4 (ranging from 89 to 76) in normals, whereas in the cases of hyperthyroidism it was 237.3 μg T_4, in hypothyroidism 13.18 μg T_4, in chronic liver diseases 73.07 μg T_4, in liver cirrhosis 77.1 μg T_4, all in average. However, no significant difference was observed between the normal control and the patients of liver diseases.

Kinetic analysis was carried out principally following the methods of CAVALIELI (1966) by assuming 2 compartments, plasma and liver in the

distribution of the tracer (10). As a result the following values were obtained: 1) in normal controls (5 cases): hepatic T_4 distribution volume (H), 3.00 ± 0.671; the rate constant for outflow from the liver ($_{22}$), $0.0104\pm0.0012\ min^{-1}$; the rate constant for inflow to the liver ($_{21}$k), 4500 ± 775; and the hepatic T_4 clearance (CH), 31 ± 6ml/min. 2) liver cirrhosis (9 cases): H 0.9 ± 0.6l, $\lambda_{22}0.0177\pm0.0067\ min^{-1}$; λ_{21}k, 1960 ± 648; and CH, 14 ± 8ml/min. 3) chronic hepatitis (11 cases): H, 1.08 ± 0.42; λ_{22}, 0.0159 ± 0.0032; λ_{21}k, 2300 ± 735, and CH 16 ± 4. 4) hyperthyroidism (5 cases): H, 3.02 ± 0.91; λ_{22}, 0.0123 ± 0.0022; λ_{21}k, 3800 ± 600; and CH, 37 ± 9.

DISCUSSION

We examined the dynamic distribution and metabolism of thyroxine in peripheral organs by assuming a three-compartment model. The time dependent curve for the second pool in terms of $Q_2(t)$ fitted well to the experimental data of counting of the liver radioactivity by analog computer (Fig. 3). $Q_2(t)$ was represented by $L_{(t)}-(Q_1(t)/Q_1(0))L(0)$ which was corrected by correcting coefficiency ($V_L ED$) obtained from experiment of phantom (Fig. 2). However, it is necessary for us to consider a possibility that a minimal amount of the conjugated thyroxine and deiodinated thyroxine in the kidney might have entered into the curve of $Q_2(t)$. Admitting it possible, we should separate the pool of metabolism into two parts by addition of $Q_4(t)$.

ALBERT and KEATING (5) found that in the rat nearly one-third of the dose was taken up by the liver within one minute. CAVALIERI *et al.* (1) stated that in the dog 12% of the dose accumulated in the liver by 60 minutes after injection, and also in human the liver played an important role in the distribution of T_4. FRIIS (6) estimated that 25 to 30% of the dose of labeled T_4 was taken up by the liver within one hour in normal humans. POCHIN (5), using a method of profile body scanning, has estimated that nearly one-half of injected dose of $^{131}IT_4$ was localized in the liver within 2 hours after administration. The calculated hepatic T_4 distribution volume in seven normal subjects averaged 5.21 ± 0.7, according to POCHIN (5), 3.801 ± 5.0 by CAVALIERI (1) which consisted of nearly one-third total T_4 distribution volume, and $3.42\ l\pm0.2$ by the author. CAVALIERI has reported that if a normal hepatic mass of 1400 g was assumed, the concentration ratio of unlabeled T_4 in liver (in μgT_4 per g) to that in plasma (in μgT_4 per ml) on average is nearly 3 to 1. This fact indicates that thyroid hormone is largely taken up positively by the liver tissue. We reported pre-

viously the cases of decreased TBG with normal liver function, one of which showed one half or less than the normal mean in T_4 distribution volume in blood (9). In constrast, the increase in the T_4 distribution volume was remarkable in the liver, assuming that in such a case TBG would be lacking in the liver as well as in plasma, CAVALIERI (1) using the same method of T_4 turnover study, estimated similar results in two cases with decreased TBG and he stated that TBG would not play an important role in the binding with T_4 within the liver. It is likely, therefore, that most of the intrahepatic T_4 is reversibly bound to the sites on or within the liver cells.

It has been demonstrated that in the cases of liver diseases, hepatic pool size and hepatic distribution volume are remarkably reduced (Fig, 5), which are consitent with the results obtained by CAVALIERI (1) and OPPENHEIMER (2). In liver the P'_2 was approximately one-half the control mean 216.3 mgT_4, P'_3 was nearly twice and urine excretion of T_4 was twice the control mean inspite of normal value of P'_1. These results are consistent with the fact that, when we take the time dependent photogram after the intravenous injection of 150 μCi of ^{131}I-T_4 using Scinti camera (product of Nuclear Chicago Co. Ltd.). A higher radioactivity is observed in the field of the kidney of those cases with liver cirrhosis and a lower activity in the field of the liver than in normal controls, while in controls the radioactivity in the field of the kidney can hardly be observed. The values of the excretion of thyroid hormone do not change in the cases of the liver diseases, because the total volume of excretion into the urine and bile are almost equal both in normal cases and in the diseases of the liver. The average value of urinary excretion is slightly elevated in the cases of the liver cirrhosis and that of biliary excretion slightly decreased. In contrast, the urinary excretion of ^{131}I-T_4 is decreased more markedly in the cases of decreased TBG than in normal subjects (9). These phenomena are interpreted on the basis of kinetic analysis of a three-compartment model as follows. The liver plays an important role in the distribution of T_4, so long as the liver functions normally. The liver pool of T_4 is enlarged to compensate the decreased plasma pool due to low serum concentration of T_4 in decreased TBG, the liver may be regarded as a buffer that acts to moderate abrupt changes in the level of circulating hormones.

Since in the liver cirrhosis, on the contrary, the liver pool of T_4 is decreased, thus values of biliary excretion of T_4 decreases, the other pool size of T_4 enlarges compensatorily in order to maintain the concentration of plasma T_4 within the normal range, assuming that the urinary excretion of ^{131}I-T_4 is elevated.

CONCLUSION

By assuming a three-compartment model, kinetic analysis of peripheral thyroxine distributions in various organs was represented by the values calculated on the basis of the disappearance curve of ^{131}I-T_4 radioactivity in the serum, time dependent curve of radioactivity over the liver and urinary excretion of ^{131}I-T_4 in attempts to clarify the kinetic distribution of the thyroxine and the time dependent pool size of thyroxine in each compartment such as serum pool, liver pool, and the other pool,

As a result it has been demonstrated that pool sizes of thyroxine, in the serum, liver and the other pool are enlarged in hyperthyroidism, while they are decreased in hypothyroidism in respective pools.

We have recognized the reduction in the values of the liver pool size of ^{131}I-thyroxine and ^{131}I-thyroxine excretion into the bile, while the increase of ^{131}I-thyroxine excretion into the urine in the cases of chronic hepatitis and cirrhosis of the liver, but the thyroxine concentration in the serum to remain within the normal level in liver diseases. As a result of the reduction in the liver pool size of ^{131}I-thyroxine and in its uptake into the liver, the other pool size enlarges to compensate the reduction and the function of the other pool is elevated.

APPENDIX

In formula (4) these equations may be solved by use of the Laplace transformation under the initial condition where $Q_1(0)$, $Q_2(0)$ and $Q_3(0)$ is equal to zero. They are to be replaced by

$$\begin{aligned}
&(S+k_{11})Q_1(s) - k_{12}Q_2(s) + k_{13}Q_3(s) = \rho_1 \\
&-k_{21}Q_1(s) - (s+k_{22})Q_2(s) = 0 \\
&-k_{31}Q_1(s) + (s+k_{33})Q_3(s) = 0
\end{aligned}$$

Hence, by Crammer's rule

$$Q_1(s) = \frac{N(s)}{D(s)} \qquad \cdots\cdots(7)$$

where $N(s)$ is the numerator and the $D(s)$ is the denominator of $Q_1(s)$

$$N(s) = \begin{vmatrix} \rho_1 & -k_{12} & -k_{13} \\ 0 & s+k_{22} & 0 \\ 0 & 0 & s+k_{33} \end{vmatrix} = \rho_1[s^2 + (k_{22}+k_{33})s + k_{22}k_{33}]$$

$$D(s)=\begin{vmatrix} s+k_{11} & -k_{12} & -k_{13} \\ -k_{21} & s+k_{22} & 0 \\ -k_{31} & 0 & s+k_{33} \end{vmatrix} = s^3+(k_{11}+k_{22}+k_{33})s^2+(k_{11}k_{22}+k_{22}k_{33}+k_{33}k_{11}$$

$$-k_{13}k_{31}-k_{12}k_{21})s+k_{11}k_{22}k_{33}-k_{13}k_{31}k_{22}-k_{12}k_{21}k_{33}$$

The Laplace transformation of the formula (1) is as follow:

$$Q_1(s)=\frac{A_1}{S+\alpha}+\frac{B_1}{S+\beta}+\frac{C_1}{S+\gamma}$$

$$=\frac{(A_1+B_1+C_1)S^2+[A_1(\beta+\gamma)+B_1(\alpha+\beta)+C_1(\alpha+\beta)]S+A_1\beta\gamma+B_1\alpha\gamma+C_1\alpha\beta}{S^3+(\alpha+\beta+\gamma)S^2+(\alpha\beta+\beta\gamma+\gamma\alpha)S+\alpha\beta\gamma} \quad \cdots(8)$$

As the formula (7) is equivalent to the formula (8) it may be applied to the method of undeterminate coefficient between both formulas, then obtain

$$\frac{A_1(\beta+\gamma)+B_1(\alpha+\gamma)+C_1(\alpha+\beta)}{A_1+B_1+C_1}=k_{22}+k_{33}$$

$$\frac{A_1\beta\gamma+B_1\alpha\gamma+C_1\alpha\beta}{A_1+B_1+C_1}=k_{22}k_{13}$$

$$\alpha\beta+\beta\gamma+\gamma\alpha=k_{11}k_{22}+k_{22}k_{13}+k_{13}k_{11}-k_{13}k_{31}-k_{12}k_{21}$$

$$\alpha\beta\gamma=k_{11}k_{22}k_{13}-k_{13}k_{31}k_{22}-k_{12}k_{21}k_{13}$$

$$\alpha+\beta+\gamma=k_{11}+k_{22}-k_{13}$$

here $k_{11}=k_{01}+k_{21}+k_{31}$, $k_{22}=k_{12}+k_{01}$, $k_{33}=k_{13}$

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