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Molecular Exchange and Blood Perfusion through Tissue Regions*

By HARDIN B. JONES

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The distribution of the circulating blood is marked by great differences among the many regions of the body. The visceral tissues—the liver and organs of the portal drainage, the kidneys, the brain, the secretory glands, the heart, lungs and bone marrow amount to approximately ten percent of the body weight, but they receive collectively the bulk (80%) of the cardiac output. The remainder of the body (the carcass) which is composed chiefly of skin, muscle, fat and bone can be expected to be perfused by less than an average of 0.025 liters of blood per liter of tissue per minute. This is in contrast to the perfusion of the visceral tissues, the average of which is approximately 0.5 liters of blood per liter of tissue per minute at rest.

I. Gas Exchange Studies

Inert gases are found to move into and out of the body at comparable rates (Table I). Since their relative behaviors are the same within limits of measurement (approximately 5%), the process of diffusion or permeation of the extravascular space must be considered to be rapid compared to the basic limitation of the perfusion of blood through the tissue capillaries as far as exchange of these simple substances is concerned; and the time constant, k, of the exponential exchange has been shown to be equivalent to the blood perfusion factor through the tissues (see equation 4).

1. Gas Exchange Equation of the Whole Body

The general form of the gas exchange equation is the sum of several independent exponential parts; the number of components has varied

* Contribution from Division of Medical Physics, University of California, Berkeley, California.

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in the past according to investigator and experimental conditions. The equation for whole body accumulative nitrogen elimination during oxygen inhalation reported by Behnke (1) has two parts:

$$N_i \text{ (liters)}^* = 0.364\, L(1 - e^{-0.09M}) + 0.50\, L(1 - e^{-0.008M}) \quad (1)$$

The equation was suggested by him to represent the exchange rates of the water and the fat phases of the body respectively. When the nitrogen elimination curve can be followed more precisely and for longer periods

TABLE I

Whole body exchange of inert gases measured for two inert gases during the same experimental time. Results are given in terms of the time constants of the equation: $R = R'e^{-k_1t} + R''e^{-k_2t} + R'''e^{-k_3t}$

	k_1	k_2	k_3	k_4
N_2	0.69		0.022	
Kr	0.69		0.022	
N_2	0.49		0.028	
He	0.49		0.025	
N_2	0.45	0.085	0.020	?
Kr	0.40	0.090	0.019	?
N_2	0.53	0.097	0.020	0.0078?
He	0.50	0.094	0.022	0.00 ?
N_2*	0.46	0.087	0.024	0.0047
Xe*	0.35	0.087	0.024	0.0038 .0008

* Determined simultaneously using radioactive xenon.

of time, it can be found that there must be added at least one more component (11) and the equation becomes (approximately for a 70 kilo man):

$$N_i \text{ (liters)} = 0.10\, L(1 - e^{-0.4M}) + 0.5\, L(1 - e^{-0.04M}) + 0.5\, L(1 - e^{-0.00M}) \quad (2)$$

The equation represents, approximately, in sequence: (a) the viscera and highly vascularized segments of the body, (b) the carcass tissues except adipose tissue and (c) adipose tissue. Still more care in the resolution of nitrogen exchange gives the following approximate equation:

$$N_i \text{ (liters)} = 0.1\, L(1 - e^{-0.4M}) + 0.17\, L(1 - e^{-0.1t}) + 0.4\, L(1 - e^{-0.02t}) + 0.5\, L(1 - e^{-0.00M}) \quad (3)$$

The fourth and last component again can be identified as the exchange in adipose tissue from experiments in which two gases of different water/

* At standard conditions.

fat solubility ratio are used. The third component is in agreement with the values obtained from the rates of saturation of radioactive gases (measured by γ-ray detection at the surface of muscle masses of the body) which have been observed to vary from 0.03 to 0.010 min.$^{-1}$ fractional gas exchange or blood perfusion rate, measured as volumes of blood per volume of tissue per minute. The first components of the nitrogen elimination equation are difficult to observe because of the washing out of traces of nitrogen in the lung gas spaces. Organs and tissue segments whose perfusion is greater than 0.5 min.$^{-1}$ cannot be separated from the events of mixing of gases in the lung spaces (see Table II). In this

TABLE II

Regional Perfusion Rates in Man (~ 70 Kilo)

	Vol. blood/vol. tissue/min.	Liters of blood/min.
Thyroid (10, 20, 25)	3.0 to 10.0	0.10
Kidney (24)	5.0	1.33
Brain (14, 15, 11) 1.4 / 0.35	0.50	0.76
Marrow (11)	0.15	0.30
Liver (11, 6, 3)	1.10	1.60
		4.09
Estimated for heart (0.15 liters/min.) and for 100 g. of small glands (testis, prostate, adrenals, salivary gland) estimate 0.05 liters/min.		0.20
		4.29 liters/min.

Direct Fick in man estimated at 5.89 liters/min. (4)

Blood perfusing muscle, skin, fat and bone should average

$$\frac{5.89 - 4.29 \text{ liters/min.}}{\sim 60 \text{ liters of tissue}} = 0.026 \text{ Vol. blood/vol. tissue/min.}$$

"Average" perfusion of resting muscle 0.01 to 0.030	Av. 0.021 per min.
"Average" perfusion of adipose tissue	0.021

Mixing rates of the pulmonary gas volume during normal quiet breathing

	Rapid rate	Slow rate
Volume of respiratory gas	2.3 ± 0.8 liters	0.71 ± .09 liters
Half-time of equilibration	0.45 ± 0.13 min.	1.6 ± 0.4 min.
Time constant, k, of equilibration	1.55 ± 0.49/min.	0.44 ± .10/min.

category are parts of the brain, parts of the liver, the kidneys, the thyroid, and possibly other small regions of the body. Estimation of the "cardiac output" from the summated whole body nitrogen elimination data by estimating and summating regional tissue perfusion is usually 1.5 to 2 liters per minute less than the average accepted amount of the cardiac output at rest. A compensating error, dilution of exchanging foreign gases into lung regions of slowly mixing gas spaces, is a possible explanation for the general agreement between the foreign gas methods of cardiac

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output and the direct Fick method (11). Foreign gas methods of estimating cardiac output should become relatively more reliable during exercise due to the fact that most of the increase in cardiac output is in the muscle whose blood perfusion factor is considerably less than 0.5 min.$^{-1}$

2. *Gas Exchange Measurement*

Methods of radioactive gas exchange measurements have been previously described (11, 29). They differ from classical methods only in the substitution of relative radioactivity for relative concentration of the substance studied. Gamma emitting inert gases, N, A^{39}, Kr^{85}, and Xe^{133} have been used to measure the exchange between the lungs and the tissues and between the tissues and the lungs. Identical results are obtainable either in saturation or desaturation of a tissue, if the equations are fully resolved in fitting the experimental results and if during saturation the concentration of the gas in the lungs is maintained constant (11, 29). In either saturation or desaturation of tissues, the gas exchange rate $\left(\frac{dA}{dt}\right)$ of a quantity of gas, A, exchanging between a tissue segment and the lung gas space is described in the simplest form:

$$\frac{dA}{dt} = kAe^{-kt} \tag{4}$$

but usually there are two or more independent components

$$\frac{dA}{dt} = k'A'(1 - e^{-k't}) + k''A''(1 - e^{-k''t}) + k'''A'''(1 - e^{-k'''t})$$

The quantity exchanged, A_t, is described in the simplest form:

$$A_t = A(1 - e^{-kt}),$$

but usually

$$A_t = A'(1 - e^{-k't}) + A''(1 - e^{-k''t}) + A'''(1 - e^{-k'''t}) \tag{5}$$

At zero time $\frac{dA}{dt} = kA$. This value kA is usually obtained from a plot of the differential form of gas exchange measurements; A may be calculated as $\frac{kA}{k} = A$. Conventional methods of analyzing exchange rates have taken the form of plotting the log of $\frac{dA}{dt}$ or $\frac{dA}{dt}$ on a logarithmic scale against *time* on a linear scale (see Fig. 1). Frequently, $\frac{dA}{dt}$ is obtained directly as the experimental measurement. Examples: a) the quantity of dissolved nitrogen collected at successive time intervals during nitrogen elimination period, b) urinary collections of radiosodium, iodide, etc., for

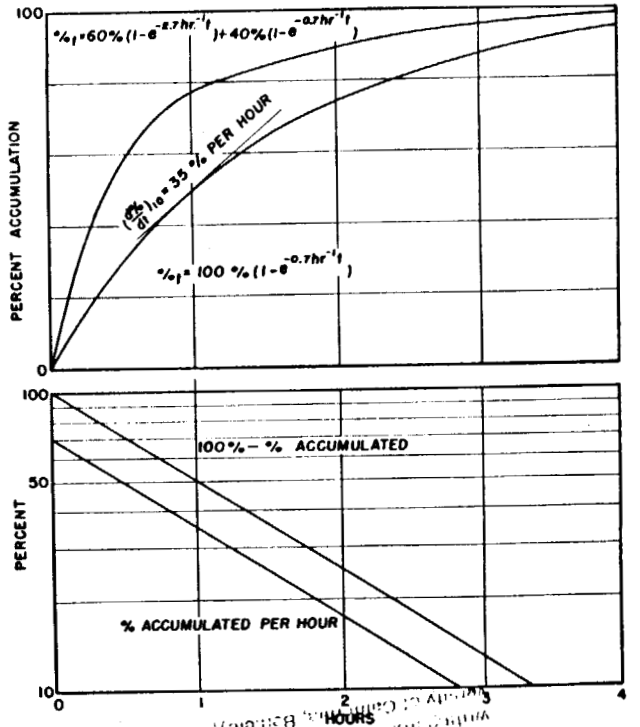

FIG. 1

Schematic curves of accumulation of a defined amount of radioactive material. The upper curves show a single component and also a two-component exponential equation of accumulation. On the lower graph, the single exponential equation is shown on a semilogarithmic scale which resolves the curve to a straight line function from which the half-time can be read conveniently (1 hour) and converted into $k > 0.7$ hour^{-1}. Also drawn on the semilogarithmic scale is the differential form of the equation which may be obtained from the cartesian graph above by measuring the tangent at any point. The tangent at 1 hour is shown above as 35% hour^{-1} on both graphs.

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short measured periods. The time constant, k, of exponential change or exchange rate is conveniently measured in appropriate data as the reciprocal of the time to reduce a given rate or a given amount, A, to $1/e \times A$. More conveniently, k is measured as the time to reduce a given rate or amount A to $\frac{1}{2} \times A$, the half-time, which if divided into $\log_e 2$ equals k; or $\frac{k \log_e 2}{\frac{1}{2}\text{ time}} = \frac{0.693}{\frac{1}{2}\text{ time}} = \frac{1}{1/e\text{ time}}$. Sometimes, the quantity A is definitely known, that is, it will represent an original aliquot and will be entirely concerned with the exponential processes measured. In these cases, it is possible to analyze data by plotting log A against time. If, however, A is estimated from an amount of material administered and if part of A either remains fixed or has pathways of removal outside of the considered measurements, then if the amount that will eventually pass through the measured rate process, A_∞, is estimated as the amount administered, A, erroneous conclusions will be made from semilogarithmic analysis as to reaction quantities and rates. For this reason, it is not advisable to plot, in semilogarithmic analysis, $\log \frac{A_t}{A_\infty}$ or $\log (A_\infty - A_t)$ against time in an effort to establish the time constant of the exponential rate processes. It is better to differentiate data which are collected as accumulated amounts of exchanged material of the type: $A_t = A_\infty (1 - e^{-kt})$ so that A_∞ will not have to be estimated from the amount that is supposed to be exchanging but rather from $\frac{dA}{dt} = kA_\infty e^{-kt}$ in which the effective A_∞ is estimated as the rate at extrapolated time, zero, divided by k, $\frac{dA/dt}{k} = A_\infty$. This is particularly advisable when the exponential exchange reaction may comprise more than one component of exchange rates and in cases in which it is not possible to follow the process to completion.

3. *Regional Gas Exchange and Blood Perfusion*

As stated above, the gas exchange rates of the tissues are essentially determined by the blood perfusion rates, and except for gas exchange in adipose tissue, in which the exchange rate is slowed by the ratio of gas solubility in blood/solubility in the tissues, the perfusion rate is identical with the exponential gas exchange constants. Rarely does a situation exist in the tissues, however, in which a single tissue has such precisely uniform perfusion throughout, that a single exponential component $A_t = A_0 e^{-kt}$ can describe the exchange events. Results are usually indicative of at least two degrees of blood perfusion which are detectable as different exchange time constants in exchange equations of two or more

components. Most of the tissues, however, are uniform in their perfusion to the extent of 70 to 95% following a single exponential exchange rate. These values are referred to as the *modal* exchange or modal perfusion of the tissue; small segments of much higher perfusion rates are sufficient to bring the average blood perfusion of the extremities from a modal perfusion of 0.019 min.$^{-1}$ to an integrated average of 0.070 min.$^{-1}$ In the thigh and the leg, there is little difference between average and modal values which are estimated from radiokrypton exchange to be:

	Average perfusion	Modal perfusion
Hand	0.070	0.025
Leg	0.019	0.014
Thigh	0.026	0.019
Fat	0.021	0.019

Blood perfusion through the hand is representative of the remainder of the body carcass except that there is a relatively great segment of highly vascularized tissue which presumably is skin. Values for blood perfusion through the hand that have been obtained from exchange of radioactive krypton and argon and nitrogen are as follows:

No. Subjects	Intensely perfused region		Modal region		Fat and least perfused region		
	Per cent of the hand	Perfusion rate Vol. blood/min./vol. hand	Per cent of the tissue	Perfusion rate Vol. blood/min./vol. tissue	Per cent of the hand	Fat perfusion rate Vol. blood/min./vol. tissue	Least perfused region Vol. blood/min./vol. tissue
9	14.5%	0.17	79.1%	0.021	6.4%	0.020	.004
11	14%	0.23	80%	0.025	6%		

When the hand is warm and flushed as in exercise, or when the hand is warmed, the circulation increases, values of perfusion rates of 1.7 min.$^{-1}$ for 40% of the hand tissues have been observed during exercise in which case the modal tissue (chiefly muscle) increases to 0.05. When the hands are cold, less than 27°C. skin temperature, as little as 1% of the tissues of the hands may be intensely perfused. In this state, the modal tissue of the hand remains little changed, the blood perfusion decreasing to 0.015 min.$^{-1}$ from usual perfusion factors of 0.021–.024 min.$^{-1}$

Estimation of the perfusion rates of adipose and fatty areas of the body has been calculated from direct measurement of the exchange of

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radioactive gas in superficial fat pads and by comparison of whole body exchange of nitrogen, krypton and xenon. These values are as follows:

	Modal k, nitrogen exchange/min.	Blood perfusion = $k \times \frac{\text{solubility in blood}}{\text{solubility in fatty tissues}}$*
Man, rest	0.0047	0.015 to 0.025
exercise	0.0042	
Cat anesthetized (data from Whiteley) (29)	0.0046	
	0.007	

* Assuming fat/water solubility ratio of 5 and that the adipose tissues are 60 to 85% fat.

Adipose tissue is largely composed of fat droplets, hence the vital tissue has an effective perfusion of 0.06 to 0.12 when the adipose tissue is corrected for its dilution by nonvital fat. The perfusion of blood through adipose tissue is not strictly uniform in terms of the pattern of open capillaries (Gersh, 9), and by consideration of the fact that gas exchange of body fat is at least a two component exponential expression. The modal nitrogen exchange of fatty tissue approximates 0.005 min.$^{-1}$ Two to six per cent of such adipose tissue may have gas exchange of the order of 0.05 min.$^{-1}$ and a corresponding perfusion rate of about 0.2 min.$^{-1}$

Blood perfusion through the brain has been estimated by gas exchange (14, 15, 11). The method of Kety (14) has made use of the exchange of dissolved nitrous oxide between blood and cerebral tissue. The general value of 0.76 liters through the cerebral tissues per minute (14, 15) is verified by exchange rates of radioactive krypton, except that the radioactive krypton exchange is indicative of two rates of gas exchange or perfusion of blood through the cerebral tissues. There is great difficulty, however, in eliminating the lung gas mixing effects which are reflected in the arterial blood concentrations of the inert gas procedures. Kety's method circumvents this difficulty by making use of the integrated difference in concentration of arterial blood and jugular blood during the short period of inhalation of nitrous oxide. The measurements as a phenomena of inert gas equilibration are not sufficiently prolonged to permit easy resolution into more than a single exponential saturation component. Attempts of this sort to fit exchange processes which are more complex than a single exponential component, lead to an assumption that the time constant, k, of the exponential term is changing with experimental time. A similar paradox was encountered by Behnke (1) in attempting to fit nitrogen exchange to a two component exponential equation. The "changing" time constant, k, can be stabilized in Kety's measurement by

fitting the data with two components instead of a single one. This indicates that the possible pattern of cerebral circulation is such that about 18% of the cerebral tissue is perfused with 1.4 volumes of blood per volume of tissue per minute and 82% has a perfusion rate of 0.35 min.$^{-1}$ The effective average is the value calculated by Kety, 0.54 min.$^{-1}$, which has been calibrated against direct flow methods within the range of the variable time constant. Current techniques will probably not permit a reliable resolution of the cerebral gas exchange data to two components as a routine testing procedure. In the brain and in areas of muscle and fat in which blood perfusion is estimated from the exchange of substances, there is practically always evidence for two or more perfusion rates. These perfusion rates do not necessarily conform to gross regions of different anatomical structure, but probably have most relation to the random pattern of the open capillaries, which have average uniformity, but here and there by coincidence of overlapping capillaries there are zones of much more intense circulation than the modal perfusion of the tissue.

II. Other Molecular Exchange Studies

1. *Iodide Exchange and Thyroid Blood Perfusion*

All estimates of the perfusion of blood through the thyroid gland have placed it as one of the most intensely perfused tissues:

	Perfusion rates
Means (17) man	3.0 to 4.0 min.$^{-1}$
Jones (11, 10) minimum in the rat	3.0 to 10.0 min.$^{-1}$
Myant, Pochin, Goldie (21) minimum in man	0.5 to (15.0 min.$^{-1}$, hyperthyroidism)
Stanley (25)—minimum in normal man	0.25 to 1.0 min.$^{-1}$

Values in the latter two references are calculated from the rate of uptake of radioactive iodide from the circulating blood. In rats, mice and in man, intravenously administered iodide appears to be rapidly distributed between the blood and an extravascular space (the iodide space). This space varies considerably as evidenced from the displacement of the labeled iodide concentration of the various tissues from one another (Fig. 2). The soft tissues remain in equilibrium with blood iodide, as evidenced from the remarkable parallelism of the various tissues in the rats (Fig. 2). Thus, the iodide in this space is likely freely exchangeable.

The concentration of labeled iodide in all of the tissues (except the thyroid) can be expressed by the equation: $[I]_t = [I]_0 e^{-kt}$. The concentration of iodide varies but the rate of disappearance of the labeled

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iodide, k, is the same for all of these tissues. It is probable that the iodide space is essentially different from the sodium space or the extravascular space. Also, about 45% of blood iodide is associated with the

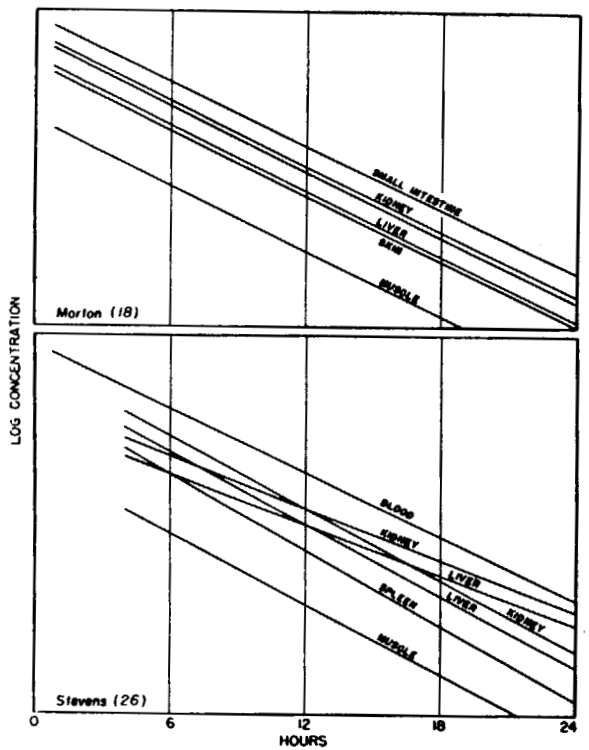

FIG. 2

The labeled iodide content of the various tissues in the rat are parallel showing a single exponential disappearance from the iodide space. Data taken from Morton (18) and Stevens (26).

cells (Jones). It has been shown by Myant *et al.* (20) and Jones (unpublished) that the urinary excretion of iodide and the thyroid uptake together determine the removal of labeled iodide from the iodide space. Indeed, the simultaneously obtained experimental curves they have

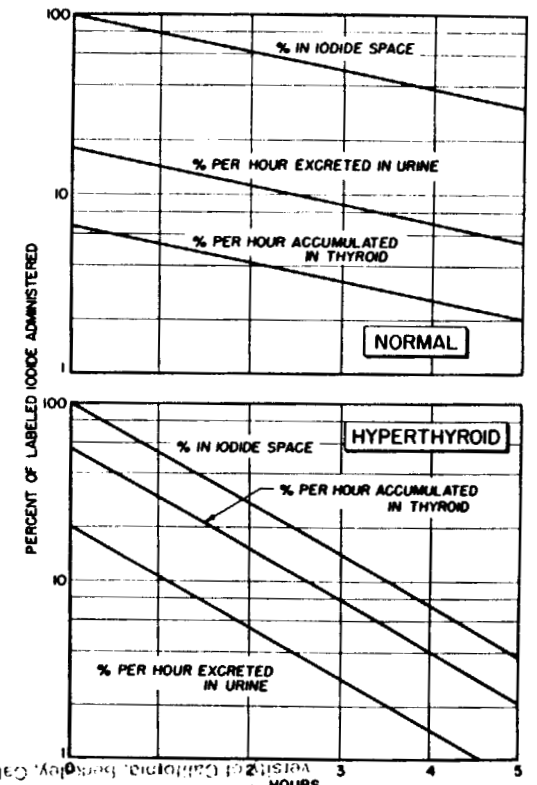

FIG. 3

The exponential distribution with time of administered labeled iodide between iodide space, the immediate accumulation in the thyroid and the immediate excretion in the urine. This data is calculated from graphic curves given by Myant, Pochin, and Goldie (21).

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given (20) can be analyzed for the initial events of iodide labeling in man as follows:

Hyperthyroid subject	
Accumulated % of administered labeled iodide in urinary excretion	$= \%_t = 14(1 - e^{-0.011\ \text{min.}^{-1}t})$
Accumulated % of administered labeled thyroid uptake of labeled iodide	$= \%_t = (87)(1 - e^{-0.011\ \text{min.}^{-1}t})$
Plasma concentration of labeled iodide	$\%/\text{liter}_t = 4.0\%/\text{liter}\ (1 - e^{-0.011\ \text{min.}^{-1}t})$
Normal subject	
Accumulated % of administered labeled iodide in urinary excretion	$\%_t = 73(1 - e^{-0.0041\ \text{min.}^{-1}t})$
Accumulated % of administered labeled thyroid uptake of labeled iodide	$\%_t = (27)(1 - e^{-0.0011\ \text{min.}^{-1}t})$
Plasma concentration of labeled iodide	$\%/\text{liter}_t = 4.5\%/\text{liter}\ (1 - e^{-0.0041\ \text{min.}^{-1}t})$

These exponential equations were obtained by fitting the labeled iodide fraction of these three regions containing labeled iodide simultaneously for the first two hours only, and the equations were so parallel that they cannot be in experimental variance with the data by more than ±2%; they have all been given the same value as simultaneous fitting seems to be justified (Fig. 3). The radioactive iodide, during the period immediately following iodide administration, may be accounted for between the thyroid, the urinary excretion and the iodide space (Myant *et al.*, 20), and this was also the basis of thyroid calculation from data of uptake of iodide in the rat thyroid (11). In man and in the rat, there is an obvious inverse relationship between the thyroid uptake and the renal excretion. The rats that were used to estimate the minimum circulation to the thyroid from labeled iodide uptake, gave values of thyroid perfusion of 3.0 to 10.0 min.$^{-1}$ (11, 10) without taking into account urinary excretion of labeled iodide which was less than 10% in two hours in these animals. Thyroid circulation was calculated roughly as follows: 2 to 5% of injected tracer radioactive iodide was found in the thyroids in 12 minutes. Other rats sacrificed at one hour had a maximum of 20% and a minimum of 11% in the thyroids. Values from 10 minutes to 2 hours on semilogarithmic plottings were consistent with a continuous exponential uptake. Hence, the 12 minute values should have been little affected by delays in mixing of the iodide space. This mixing process appeared to be very rapid and the blood was in equilibrium with an iodide space equal to 28% of body volume, determined by extrapolating blood concentration to zero time. Also, during this period urinary excretion appeared to be negligible. Assuming complete clearance of iodide from blood that perfused through the thyroid gland, the minimum perfusion rate of the thyroid in the rat was roughly calculated to be:

$$\frac{\text{2 to 5.5\% of the iodide space perfused as blood through the thyroid}}{\text{12 min.}} = \frac{(2 \text{ to } 5.5)(0.28 \text{ iodide space})(200 \text{ g.})}{12} = 0.092$$

to 0.27 g. of blood through the thyroid per minute; since the average weight of the thyroids was 0.030 g., the minimum perfusion of blood through the thyroid was reported as 3.0 to 10.0 min.$^{-1}$

Urinary excretion can only affect the above estimation by the fraction excreted in that period and this was negligible in these data. Values for thyroid perfusion were also made from calculations of the rate of disappearance of labeled iodide from the plasma and the rate of appearance in the thyroid. Both of these values were corrected for the slight urinary excretion. This method was used to calculate thyroid perfusion rates in Curtis-Dunning rats sacrificed up to two hours after intravenous injection of a tracer dose of radioactive iodide. Thyroid perfusion was found to be at the minimum in these rats: 3.3, 4.1, 4.9, 4.9, 4.9, 5.7, 8.2, 8.2, 9.0 volumes of blood per volume of tissue per minute. The average was 6.1 min.$^{-1}$ From studies of normal and hypophysectomized rats (Morton *et al.*, 19), normal and hypophysectomized rats can be compared. In spite of the similar thyroid mass and thyroxin contents in these two series, the hypophysectomized rat has an iodide uptake from the iodide space (the iodide space is also the same in the two groups) of only 1% per hour which calculates to be a minimum thyroid perfusion of 0.7 volumes of blood per volume of tissue per minute. The inorganic iodide of the thyroid of the hypophysectomized rat is parallel to the blood iodide (19) and for this reason it is probable that the slow and progressive uptake of labeled iodide is mostly due to lessened organic fixation of the iodide. Thus, the above value for minimum perfusion of the thyroid in these rats is probably greatly less than the actual perfusion rate.

The thyroxin utilization of rats is estimated at 20 to 40 μg. thyroxin iodide per day (see Table III). This means that the thyroid must add to the plasma 0.02 μg. thyroxin iodide per min. The plasma level of protein-bound (thyroxin) iodide is 0.03 μg./ml. and the minimum minute flow of blood to the rat thyroid is estimated to be 0.045 to 0.15 ml. of plasma per minute. Therefore, it seems that the thyroid must add to the blood perfusing through it 4 to 17 times the prevailing plasma concentration.

The iodide fixation requirements are low: 0.001 (man, 14) to 0.02 (rat) μg. of iodide per kg. body weight per minute or 1.4 to 2.8 μg. I/kg. per day. The plasma iodide level is so low that it is negligible compared to the organic iodide present (19, 27). The available iodide in many experimental animals frequently approaches a minimum on the basis of

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thyroid utilization of the iodide for thyroxine synthesis. Some investigators are attempting to calculate thyroxin synthesis from the amount of iodide that accumulates in the thyroid after labeled iodide administration. However, the thyroid has a considerable reserve capacity for iodide uptake within which it can retain a very efficient removal of iodide from the blood (25). Thus, in rats (200 g.), if 50 μg. iodide are given, 2% of the iodide is removed by the thyroid in two hours. Therefore, the amount of thyroxin formation is: $\frac{50\ \mu g. \times .02}{120\ min. \times 0.2\ kg.} = 0.041$ μg. I/kg./min. or 2.5 g. I/kg./hour fixed by the thyroid (see Fig. 4). Similarly, in other rats (100 g.) given a dose of 68 μg., 12% has been observed to be fixed in 4 hours or an iodide fixation rate of 0.34 μg. I/kg./min. or 20 μg. I/kg./hour which is obviously a high value.

TABLE III

Thyroxine Utilization Rates

	Micrograms of organic bound iodide used per day per kg. body weight	
(Rat) Dog[a] (28)	8.4 μg. I/kg./day	
Man[b] (16)	2.4 μg. I/kg./day	
100 g./Rat (5) bioassay with thiouracil	37. μg. I/kg./day	
200 g., Rat, calculated from turnover curves of Fig. 4	19.0 μg. I/kg./day	Minimum values from turnover of labeled organic bound iodide
	21.5 μg. I/kg./day	
	12.0 μg. I/kg./day	
	24.0 μg. I/kg./day	
500 g., Guinea pig	2.5 μg. I/kg./day	

[a] Radioactive protein-bound iodide was taken from rats that had received large doses of radioactive iodide. The protein-bound iodide was injected intravenously into dogs and the rate of disappearance measured. This value is calculated on the basis that the rat protein-bound iodide behaves the same as the native protein-bound iodide of the dog.

[b] Calculated by Stanley from the rate of disappearance of labeled iodide to the thyroid and the total amount of iodide in the plasma.

Calculation of organic iodide (thyroxin) utilization is possible in the same rats as above from the rate of disappearance of thyroid labeled iodide following a moderate dose of iodide carrier. Assuming that most of the organic iodide in the thyroid has come from administered iodide (in the 100 g. rat, 28% of a dose of 68 μg. of iodide is taken up by the thyroid and the rate of disappearance of this iodide is 165 hours half-time or 0.0042 hour^{-1}), the thyroxin formation can be estimated as

$$\frac{0.28 \times 68\ \mu g.\ I \times 0.0042\ hour^{-1}}{0.1\ kg.} = 0.8\ \mu g.\ I/kilo/hour$$

(see Fig. 5). Since in this case the thyroid probably already contained

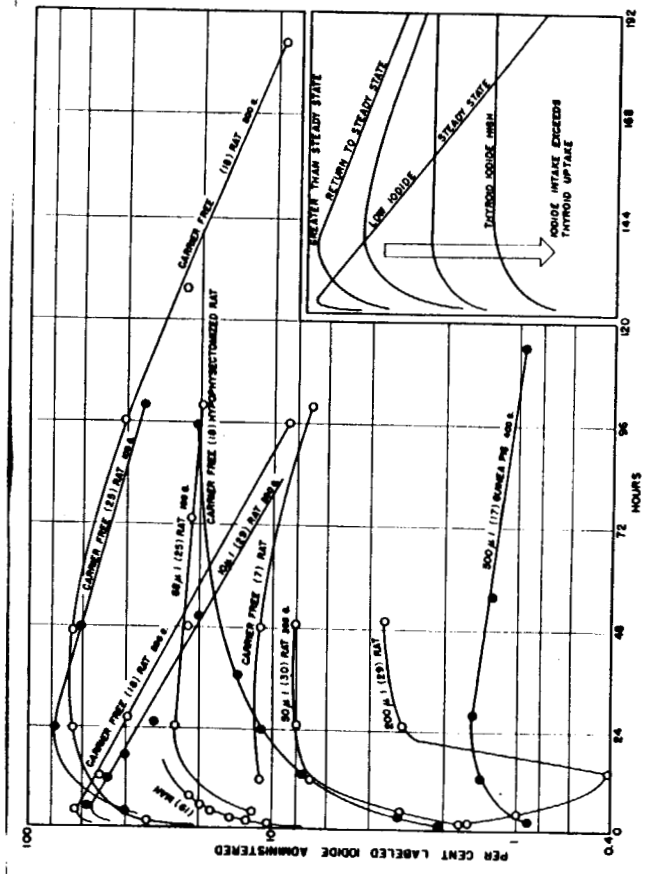

FIG. 4

Summarized data, mostly in the rat, for uptake of labeled iodide. Presumably all of these rats have (except the hypophysectomized rats) about the same fixation of iodide and synthesis of thyroxine. The differences observed are entirely explainable on the basis of varying amount of iodide in the thyroid and varying amounts of carrier iodide in the administered labeled sample with reference to the rate of synthesis of thyroxine. This is shown at the right schematically.

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about 5 μg. of iodide, the amount of organically bound iodide turned over per kilogram per hour is probably 1.0 μg. I/kg./hour. Table III gives estimated thyroxin rates from the data of Fig. 4. It is assumed that the organic iodide of the thyroid passes through thyroxin in being removed from the gland. It is further noted in Fig. 4 that the greater the total iodide content, the slower is the apparent turnover of thyroid iodide.

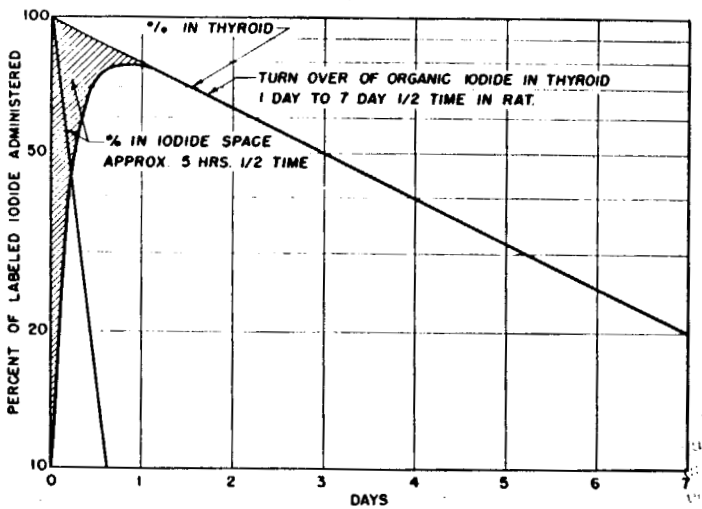

FIG. 5

Uptake and disappearance of thyroid radioactive iodide. This is a schematic curve of relative high uptake similar to those given in Fig. 4.

Obviously, all of the values of Fig. 4 are from animals whose thyroxin synthesis is comparable. The enormous spread in the accumulated labeled iodide uptake represents (1) variations in iodide content of the gland, and (2) variation in dose of iodide administered. Estimates of thyroxin formation from the size and turnover of the thyroid iodide pool are given in Table III. The turnover of labeled thyroxin can be calculated from the data given by Morton *et al.* (19) and for these animals it is 71% per day. Since the uptake of labeled iodide by these animals is rapid, followed by rapid disappearance of labeled iodide, the iodide content of these thyroids must be low (estimated 4 μg. of diiodotyrosine iodide). The data of Morton *et al.* (19) are also highly consistent with the scheme of synthesis of thyroxin from diiodotyrosine. Thus, in this instance, thyroxin formation is very approximately 14 μg. I/kg./day.

It is inconceivable that in some circumstances the concentration of iodide in the iodide space of the body is so low that the perfusion rate of blood of 10.0 min.$^{-1}$ through the thyroid would be just sufficient with maximum clearance to carry the minimum required iodide to the thyroid. At other times the blood level is probably higher. This probably accounts for the fact that at most times the minimum estimated value of thyroid circulation may be 1.0 min.$^{-1}$ or less. This latter figure could be expected if the rat contains 2 μg. in the whole inorganic iodide space and the intake per day is of the order of 20 μg. (the daily requirement for synthesis into thyroxin); a similar quantity of iodide (30 μg.) given as a single dose with tracer iodide greatly depress either the clearance of iodide or the perfusion of blood through the thyroid.

In mice, 2.0 to 2.5% of administered labeled iodide was found in the thyroid in 10 minutes. From the concentration of labeled iodide in the blood, the iodide space was calculated to be 30% of body weight. The perfusion volume per minute, therefore, must have been a minimum of between 0.024 and 0.03 ml. per minute and since the thyroid mass of these mice was 0.0021 g., the perfusion factor for the normal mouse thyroid must be at least 11.4 to 14.2 min.$^{-1}$ Much lower values have recently been obtained for both mice and rats, and it is probable that the iodide content of the feed of the animals has increased which has decreased the efficiency of iodide uptake.

As pointed out by Myant, Pochin and Goldie (21), the inorganic iodide space when labeled decreases in concentration of labeled iodide exponentially as a single component by a time constant that is equal to the combined rates at which the thyroid and the kidneys are removing iodide from the iodide space. It is apparent (21) that in such normal patients as were measured, only a fraction of the blood iodide was cleared through the thyroid. Myant *et al.* (21) and Stanley (25) have calculated minimum thyroid perfusion on the basis of plasma perfusion, assuming that only the plasma iodide is available to the thyroid. These values are quoted as follows:

Plasma clearance of iodide through the thyroid:

(25) Normals	7 to 29 ml. min.$^{-1}$	
(21) Normals	8 to 38 ml. min.$^{-1}$	16 ml. min.$^{-1}$ average
(21) Thyrotoxicosis	200 to 1390 ml. min.$^{-1}$	486 ml. min.$^{-1}$ average

These correspond to minimum blood perfusion rates (obviously low due to incomplete clearance by the thyroid) of 0.5 to 2.0 vol. of blood per volume of tissue per minute in the normal and 13.0 to 90.0 (average 32.0) min.$^{-1}$ in thyrotoxicosis; the latter perfusion factors may be too high as

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allowance was not made for the fact that the thyroids are probably enlarged. As the thyroid uptake of iodide increases in the human series reported, the clearance of iodide from the blood approaches 100% (19). This is an excellent example of the fact that the diffusion and extracapillaric transportation of iodide ion is rapid enough so that blood perfusion is still the limiting factor when the thyroid perfusion rate is greater than 10.0 min.$^{-1}$ 10). Stanley (25) has shown that when 1 mg. of iodide is given to a subject during the period of uptake of a tracer dose of iodide by the thyroid, the rate of uptake of the labeled iodide is not altered even though the plasma iodide level is changed from 0.8 to 4.0 μg.%. The only change is that the absolute rate of uptake of iodide by the thyroid increases four times, and this is additional evidence of the capacity of the thyroid to extract iodide from the blood when it is present in small amounts, and evidence also that the limiting process of accumulation under these conditions is the quantity of blood perfusing the gland.

In mice, rats and men, the iodide can be accounted for between the thyroid, the urinary excretion and the iodide space. During the first 2 hours when essentially no organic iodide has returned through a cycle of iodine metabolism, the concentration of labeled iodide in the iodide space decreases exponentially (12, 16, 23, 21):

$$[I]_t = [I]_0 e^{-\bar{K}t}$$

where $\bar{K} = k_1 + k_2$, where k_1 is the fractional rate of removal of the iodide in the iodide space by the thyroid and k_2 the fractional rate of removal by the kidneys to the urine. Since $\bar{K}$ is the same exponential constant for the accumulation of labeled iodide in the thyroid, the disappearance of labeled iodide from the iodide space, and for the accumulative appearance of labeled iodide in the urine (Fig. 3), it is apparent that the fraction of the labeled iodide removed by the thyroid from the iodide space, T_I, is

$$T_I = \frac{k_1}{\bar{K}} \text{ and } k_1 = T_I \cdot \bar{K}$$

Similarly the fraction removed to the urine from the iodide space by the kidney, U_I, is

$$U_I = \frac{k_2}{\bar{K}}$$

If appropriate dietary levels of iodide are chosen, the thyroid iodide uptake, T_I, can conveniently be measured

$$T_I = 1 - U_I \text{ and } k_1 = T_I\bar{K}$$

The minimum perfusion of the thyroid should then be measurable from the fraction of the iodide appearing in the urine, from the time constant

$\bar{K}$ which can be measured from the accumulation of labeled iodide in the urine, and from the iodide space which can be determined by extrapolation from a single determination of the blood iodide using $\bar{K}$ determined by urinary collections.

If the steady state of body iodide turnover has not been disturbed by administration of labeled iodide, the thyroid iodide uptake can be calculated from the rate of iodide excretion by the kidney and the fraction of the labeled iodide that is not excreted during the first phase of labeled iodide metabolism. For example, if the urinary output of iodide is found to be 4 μg. per hour, and if during this period of iodide collection 20% of a labeled tracer dose of iodide is found to be excreted in the first urinary exponential elimination process, then the 80% of labeled iodide will accumulate in the thyroid, and quantitatively $4\ \mu g. \times \frac{80\%}{20\%} = 16\ \mu g.$ of iodide are being synthesized to organic iodide by the thyroid per minute. If this method is used to predict thyroxine formation some effort must be made to integrate the iodide intake and elimination over a generous sampling period because the thyroid gland has the obvious property of being able to accumulate iodide when it is available and to draw on its iodide stores at other times. As pointed out above, peak uptake of iodide during its period of availability may not give an accurate prediction of the physiological utilization rate of thyroxine.

2. *Sodium Exchange*

The exchange of other substances has been considered as a method of measuring regional perfusion rates. There is an obvious similarity between inert gas exchange and exchange within the body of administered radioactive sodium ion. When sodium is injected intravenously, it quickly becomes distributed in the highly perfused regions of the body. Tissues of these regions by staying in approximate equilibrium with the blood sodium form a sodium space continuous with the blood which perfuses the next most intensely perfused tissues, *etc.* This process of sodium equilibration produces a dependent series of exponential components for the dilution of the labeled sodium in the plasma, C_p:

$$C_p = 1990e^{-1.4t} + 580e^{-0.28t} + 640e^{-0.085t} + 90e^{-0.0025t} (+ 960e^{-0.00005t} \text{ amount of sodium unexcreted}).$$

The time constants of the dilution processes are related to the perfusion rates of blood through the tissues and may be compared approximately to the gas exchange time constant. The parameters determining the values of these time constants also include the effective volume of the perfusate with reference to the sodium space that proceeds each new

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dilution component. Thus far, no one has been able to analyze these parameters so that the physiological variables in the sodium distribution constants can be made use of experimentally. A recent new approach to sodium exchange by Kety (13) circumvents the above difficulties which necessitate simultaneous consideration of the whole body equilibration of administered sodium, by measuring the disappearance of a small amount of interstially administered radioactive sodium. The disappearance of a small amount of interstitially injected radioactive sodium is entirely analogous to the situation with inert gas exchange. The sodium contents of the blood and the tissues are comparable and the exponential disappearance of sodium should be highly related to the blood perfusion rate, as it seems to be (13). The radiosodium is removed from the site by exchange of sodium in the blood against the vast pool of sodium in the body and in this respect the situation is entirely the same as in gas exchange wherein the arterial blood is kept at a constant level by exchange with the ventilated lung gases. The dimensions of the exponential time constant in the case of disappearance of sodium from the injected site should be:

$$k = \frac{\text{concentration of sodium in the blood} \times \text{volume of blood/min.}}{\text{concentration of sodium in the tissues} \times \text{volume of tissues}}$$

The concentration of sodium in the blood is approximately twice that of the tissues, whereas in inert gas exchange there is the same solubility distribution in blood and tissues. Therefore, it would be expected that the time constant of sodium exchange should be twice as rapid as inert gas exchange. This is the case; Kety (13) reports an average of muscle exchange rate of $k_{Na} = 0.050$, range 0.033 to 0.066 min.$^{-1}$; whereas the gas exchange k is 0.015 to 0.025 min.$^{-1}$ for muscle (11). It is insecure experimentation, however, to measure regional circulation at the very site where a hypodermic needle has delivered an aliquot of injected sodium. In this laboratory, Warner (unpublished) has not yet been able to get the same rate of disappearance with different injected amounts of radiosodium (the method should be independent of physical dose). This may mean that the injection has somewhat disturbed the blood perfusion of the region. These technical difficulties should be controllable. The method, however, represents a technique of great promise due to the fact that regional perfusion rates can be measured with this method rapidly and with the exposure of the subject to only very small quantities of radioactive materials.

3. *Blood Perfusion of Liver and Spleen*

Exchange of inert gas in the kidneys is too rapid to measure as a means of measuring renal perfusion (11). Special methods, however, have been

developed for measuring the regional blood perfusion through the liver and spleen using colloidal radioactive chromic phosphate disappearance rates. Intravenously administered particulate chromic phosphate of about 2.8 μ diameter is evidenced by a rapid deposition of 95 to 98% in the livers and spleens of dogs, mice, rats and man after intravenous administration. Rabbits were found to localize only 80 to 90% in the liver and spleen. The other 10 to 20% was deposited in the bone marrow. This seems to be a species difference. Other colloids (7) can be made with more specific affinity for deposition in the bone marrow in several species including man. The clearance of this colloid is greater than 85% so that liver perfusion can be measured directly from the rate of disappearance of $CrPO_4$ from the blood. Liver circulation measurements are summarized in the following table (Dobson, 6):

Animal	Minimum blood tissue perfusion factor vol. blood/vol. liver/min.	Minimum clearance through liver	Maximum blood tissue perfusion vol. blood/vol. liver/min.
Dog anesthetized*	1.2 ± 0.3	0.85	1.4
Rabbit	0.74 ± 0.12		
normal	1.12 ± 0.13	0.88	1.3
Mouse			
normal	1.4 ± 0.1		
anesthetized*	1.7 ± 0.1	0.79	2.2
Rat			
normal	1.2 ± 0.1		

* Nembutal.

Disappearance of injected chromic phosphate from the blood is approximately a simple exponential function:

$$\% \text{ in blood} = \% \text{ injected} \times e^{-kt}$$

The colloid is contained within the circulating blood until it is removed by the liver or the spleen. The time constant of disappearance in this case, k, is equal to the fraction of the circulating blood volume perfusing the liver per unit time.

Blood perfusion through the spleen has been estimated from the relative uptake of spleen to liver in sacrificed animals.

	Minimum volume of blood per volume of spleen per minute
Dogs (anesthetized)	0.8
Rabbit (normal)	4.9
Rabbit (anesthetized*)	4.7
Mouse (normal)	0.34
Mouse (anesthetized)	0.49

* Nembutal.

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III. Decrease of Regional Perfusion with Age

Vascular changes appear to take place in the body carcass, such that the average blood perfusion of the modal tissue of the carcass is decreasing from 0.025 min.$^{-1}$ at 18–20 years to 0.010 min.$^{-1}$ at 25 years. These determinations are made from the rate of nitrogen exchange from the whole body (11). They are in close coincident agreement with the rate of acquisition of protection to decompression sickness by oxygen inhalation in six separately tested groups of subjects (11). The rate at which a "bends" susceptible tissue can acquire protection to bends depends upon the rapidity of its inert gas exchange which is fixed by the tissue circulation. Nitrogen elimination measurements have not been carefully extended to groups over 25 years of age, but there seems to be a progressively decreasing perfusion rate such that 35-year-olds are estimated to have bends susceptible tissues receiving only 0.005 min.$^{-1}$ (11). To a less extent, respiratory gas exchange is also determined by tissue perfusion. Berg devised a system of measuring the speed of recovery from a mild exercise bout (2). The rate of repayment of the oxygen debt and the carbon dioxide excess clearly follows the same principles as inert gas exchange. And these rates of recovery are also highly related to age. The correlation between age and CO_2 exchange rate is $r = -0.92$, between age and O_2 exchange rate is -0.71. The oxygen recovery process is likely less reliable an index of circulation as the tissue oxygen unloading is greatly modified by the oxygen dissociation of hemoglobin. Thus, there is evidence for decreased perfusion of the carcass tissues with age both at rest and under conditions of mild exercise. It is suggestive that an important part of the so-called aging process is taking place during a very early period of adult life. Whether the circulatory change induces aging or aging produces the circulatory decrease would at this point be a philosophical question. Pace (22) has recently shown a striking decrease in exchange rate of carbon monoxide with increasing age. This effect seems to be of the same magnitude as the gas exchange tissue perfusion change with age, but there may be other factors such as hemoglobin binding as well.

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