THE KINETICS OF DISTRIBUTION OF THE FAT-SOLUBLE INERT GAS CYCLOPROPANE IN THE BODY

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ABSTRACT A kinetic analysis is made of the experimentally measured time course of respiratory uptake of the highly fat-soluble, inert gas cyclopropane by normal human subjects. The analysis is based on the well-known perfusion-limited model in which a number of body compartments are arranged in parallel with the lungs *via* the circulating blood. Three distinct body compartments are derived from the data. These are tentatively identified as: (*a*) adipose tissue (*b*) fat-poor tissue of low perfusion such as resting muscle, skin, and connective tissue (*c*) fat-poor tissue of high perfusion such as brain, heart, gut, liver, and kidney. Blood flow rates to the several compartments are also derived from the data. The rates to compartments (*a*) and (*b*) are each approximately 10 per cent of the estimated total cardiac output. The derived perfusion (blood flow rate/compartment weight) of the three compartments are in the range, respectively, (*a*) 2 to 4, (*b*) 1 to 2.5, (*c*) 25 to 75 ml/min/100 gm. Uncertainties arising from the experimental data and from simplifications of the model (neglect of lung fill-up phase of uptake and gross diffusion of cyclopropane from one tissue into another) are discussed. The present type of uptake experiment is significant for the problems of total body fat determination, of gross body composition in relation to weight change, of gross shunting of blood flow from one compartment to another, of anesthesia by fat-soluble substances, and of decompression sickness.

INTRODUCTION

The purpose of the experiments conducted by Lesser, Blumberg, and Steele (1, 2) was to determine the total body fat of living animals by uptake of the highly fat-soluble inert gas, cyclopropane. Although the method proved successful in rats, a rather fortunate difficulty was encountered in its application to human subjects. A direct calculation of the total body fat requires knowledge of the amount of cyclopropane taken up when equilibrium has occurred. In the rat, gaseous equilibrium

was observed to occur in 90 to 120 min. and only cursory observation was made of the approach to equilibrium. In human subjects, however, absorption of the gas was much slower, equilibrium not being reached even at the end of 8 hrs. As a consequence, detailed observations were made of the approach to equilibrium. In analyzing such data for a series of six normal human subjects (Figs. 1, 2)[1] to de-

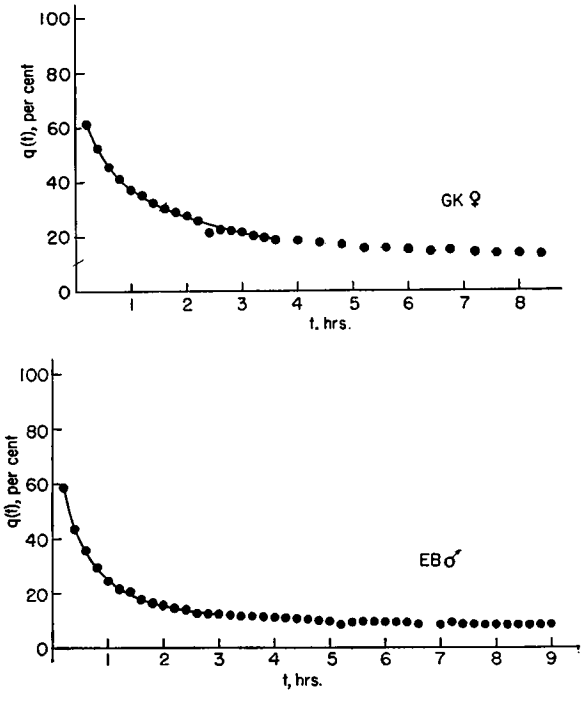

FIGURE 1*a* and *b* Cyclopropane uptake of two normal human subjects from a closed respiratory circuit. Ordinate: $q(t)$, ratio, in per cent, of amount of cyclopropane in respiratory circuit volume to total cyclopropane in subject plus external volume, at time t. Abscissa, time, t. Circles denote experimental data points. Solid lines are curves drawn "by eye" through data. Graphically measured slopes of solid line portions shown give time rate of change, $\dot{q}(t)$. Measurement of $\dot{q}(t)$ continued on solid lines drawn through data on enlarged scale of Fig. 2.

termine an equilibrium value of cyclopropane uptake (3, 4), it became apparent that a test could also be made of certain features of the well-known perfusion-limited physiological model of inert gas exchange in body tissues (5–7).

In this model (Fig. 3) the body is regarded as a group of tissues or organs each connected separately with the lungs, *i.e.*, in parallel, *via* the circulating blood (the

[1] Figs. 1 and 2 show the experimental data for two typical cases. The data for all six subjects are given in numerical form in reference 3.

liver is an exceptional case). Introduction of a foreign inert gas into the lung volume results in diffuson of this gas across the alveolar and pulmonary capillary membranes, its solution in the blood, its transport by the arterial blood into the various capillary beds, and its diffusion across the capillary membranes and throughout the extra- and intracellular tissue components. Mixed venous blood at reduced cyclo-

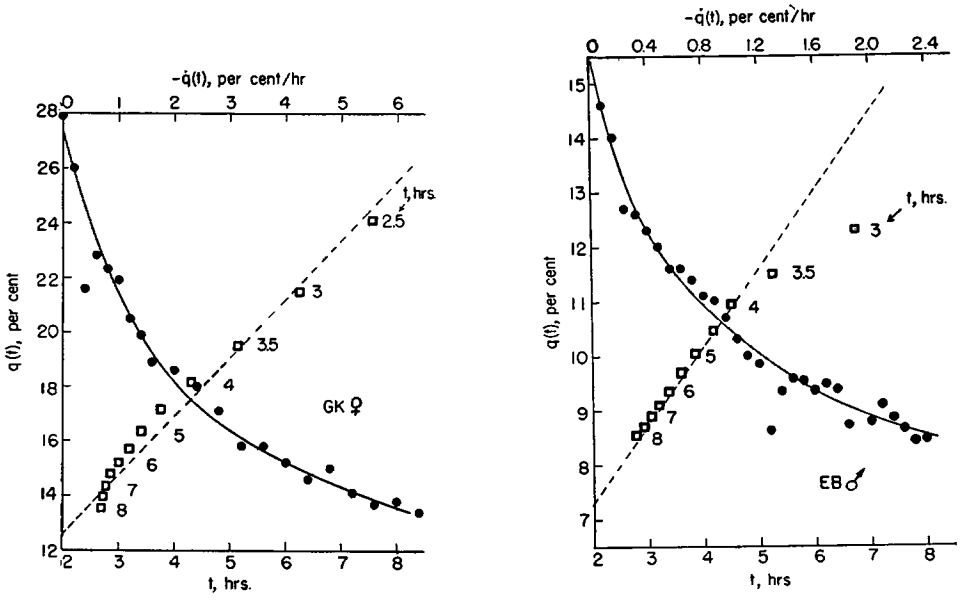

FIGURE 2*a* and *b* Circles denote enlarged plots of data of Fig. 1 in last 4 hrs. Solid lines are curves drawn "by eye" through data for graphical measurement of time rate of change of $q(t)$. Square points are plot of $q(t)$ against $-\dot{q}(t)$, the negative time rate of change of $q(t)$ (upper scale). Dashed lines are straight lines drawn "by eye" to represent the equilibrium constant q_∞ plus the slowest exponential $a_1e^{-k_1t}$ to fit the data. The q-axis intercept of the dashed line is q_∞. The slope of the dashed line is $1/k_1$. A slight displacement of the dashed lines from best visual fit with the square points was made to provide a somewhat better over-all fit of the derived q_∞ plus three exponentials to the data.

propane concentration returns to the lungs and the circulatory cycle is repeated. In this uptake process the different partial pressures of gas in the various tissues approach the partial pressure of the gas in the alveolar volume and equilibrium, or saturation, is reached when all partial pressures have become equal. Desaturation of body tissues in response to a decrease of inert gas concentration in the lungs occurs in a similar manner.

In terms of this model, respiratory measurement of rate of uptake or elimination of inert gases from the body yields information on various aspects of the transport process. If, for example, it is known or assumed that the various diffusion processes in the alveoli and in the tissues are rapid compared to the blood circulation

time, then from such measurements one can, in principle, deduce blood flow rates to the various tissues. Jones (5), in particular, has offered evidence in favor of this assumption (similar uptake and elimination rates for gases of differing diffusion constants) and has made extensive use of this model in the preceding manner. The present experiments offer a test of the model under two conditions different from those used by Jones. The gas used, cyclopropane, possesses different diffusion and solubility coefficients from the gases (nitrogen, xenon, krypton, etc.) of Jones's experiments. Secondly, a closed external rebreathing volume was employed in place of the constant external concentration arrangement of Jones.

In the following sections the calculations made from the experimental data using the above described model are described. The results are compared with existing ones, and the significance of the experiment for various physiological problems is assessed.

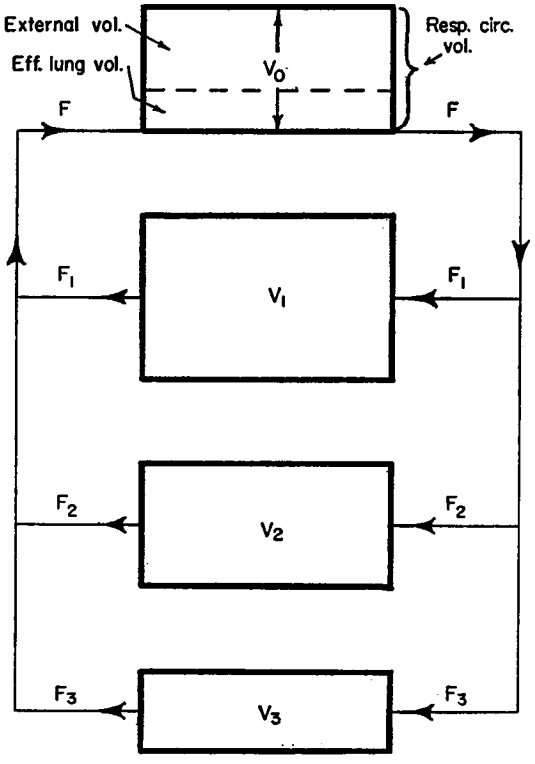

FIGURE 3 Schematic representation of physiological model. Three body compartments 1, 2, 3 are shown and a respiratory circuit compartment consisting of the external volume plus an effective lung volume. The physiological parameters of the model are: the rates of blood flow, F or F_1, through the compartments and the solubility volumes v_0 or v_1 of the compartments. The solubility volumes or "cyclopropane spaces" are proportional to the relative amounts of cyclopropane in the several compartments at equilibrium.

EXPERIMENTAL ARRANGEMENT

The experimental procedure is presented in detail elsewhere (2,3). Briefly, the subject's head and neck are enclosed by a helmet which is part of a closed respiratory circuit of known fixed volume. This volume, external to the subject, will be called the "external volume." It does not include the lung volume. Oxygen is admitted into the external volume at the rate utilized by the subject, and carbon dioxide is absorbed within it by soda lime. Pressure and temperature in the external volume are constant. A small amount of cyclopropane, to give a concentration level of the order of 1 per cent, is introduced into the external volume. At intervals thereafter, small samples of gas are withdrawn from the external volume and analyzed for cyclopropane content. In a separate experiment for each subject the "respiratory circuit volume" consisting of the external volume plus an effective lung volume (see Appendix B) is measured by a nitrogen dilution technique (2). The experimental data are expressed as the ratio $q(t)$ of the amount of cyclopropane in the respiratory circuit volume to total cyclopropane in subject plus external volume, at time t.

THE PHYSIOLOGICAL MODEL

The physiological model is considered to be a number of body compartments connected in parallel with an external compartment *via* the circulating blood (Fig. 3). Any body compartment, denoted as the ith compartment, is defined as a group of tissues, not necessarily contiguous, characterized by two quantities: a rate of flow of blood to, or blood plus lymph from, the compartment, F_i, liters/minute, and a solubility volume v_i, defined as,

$$v_i = \lambda_i V_i \tag{1}$$

in which V_i is the total volume, liters, of the compartment, and λ_i is an average solubility partition coefficient (in the sense defined below) of cyclopropane between the tissues of the compartment and blood; *i.e.*, the ratio of an average concentration of cyclopropane in the tissues of the compartment to an average concentration of cyclopropane in blood which is in solubility equilibrium with the tissues of the compartment. It is convenient to define the "solubility volume perfusion,"[2] ϕ_i, as the rate of blood flow per unit solubility volume of the ith compartment, or

$$\phi_i = \frac{F_i}{v_i} = \frac{F_i}{\lambda_i V_i} \tag{2}$$

The two independent quantities which characterize a compartment can then be taken as any two of the three quantities F_i, v_i, ϕ_i.

The anatomical justification for this physiological model is that most small pieces of tissue are presumed to be arranged in parallel; *i.e.*, a small volume of blood

[2] The term "solubility volume perfusion" is to be distinguished from the commonly used term perfusion which is rate of blood flow per unit weight of tissue.

passes through just one such piece of tissue in making one complete circuit. The parts of the body which cannot be characterized in this way, such as portions of the liver, intestinal contents, blood, and other fluids in the larger vessels, may be neglected in the present problem.[8] As can be shown from later analysis of the model, those small pieces of tissue having the same solubility volume perfusion ϕ_i have the same gas uptake rate under the conditions of the present experiment and, hence, are separately indistinguishable. Consequently, the sum of their individual solubility volumes can be considered as the solubility volume v_i of a single larger compartment and the sum of their individual spatial volumes as the spatial volume V_i of the same larger compartment. The ratio of these two volumes, v_i/V_i, defines the average implied in the definition of the partition coefficient λ_i, equation (1).

The basic relation used to analyze the model is the principle of perfuson (Fick), which states that the rate of net delivery (moles/minute) *via* the blood of a substance, in the present case cyclopropane, to a compartment is the product of the arteriovenous difference in concentration of that substance (moles/liter) and the rate of blood flow through the compartment (liters/minute). If in addition the following three assumptions are valid, a conventional compartment analysis becomes possible:

Assumption (*a*): Rate of net delivery of substance equals rate of increase of substance in a compartment. This assumption requires not only that the transported substance be not metabolized, which is apparently true for the inert gas cyclopropane, but also that it not enter or leave a compartment by any route other than the blood plus lymph. One such possible additional route in the present case is *via* direct diffusion of gas from one compartment to contiguous parts of another compartment. Thus, if a piece of muscle in compartment 2 lies next to a piece of adipose tissue in compartment 1, and the partial pressure of gas in compartment 2 increases faster than in compartment 1, gas will diffuse from the region of high partial pressure (muscle) directly across into the region of low partial pressure (adipose tissue). This compartment-to-compartment diffusion operates at distances of the order of centimeters, the presumed dimensions of gross adipose or lean tissue. This type of gross diffusion is to be distinguished from the diffusion between capillary blood and neighboring cells since the latter operates at distances of the order of 10^{-3} cm (several cell diameters).

As previously mentioned, Jones (5) has offered the observations of similar uptake and elimination rates of different gases in body tissues as evidence for the general negligibility of gross diffusion relative to blood perfusion as a kinetic mechanism for the distribution of inert gases to body tissues. However, a theoretical estimate of the rate of gross diffusion of cyclopropane into a slab of adipose tissue of

[8] Cyclopropane is about 33 times as soluble in fat as in fat-free body, weight for weight (1,3,8), so that in a normal subject in equilibrium, about 90 per cent of the absorbed cyclopropane is in the total body fat and about 10 per cent in the entire fat-free body.

thickness 1 cm indicates a non-negligible rate of uptake of gas relative to that due to perfusion. The estimate was based on a diffusion constant of cyclopropane in adipose tissue of 10^{-6} cm^2/sec. This value is indicated by the diffusion constant measurements of Davidson, Eggleton, and Foggie (9) who obtained 2.1×10^{-6} cm^2/sec. for nitrogen in lard at 25°C and by measurements in this laboratory (10) by the same method as in (9) on cyclopropane in freshly excised rat adipose tissue. Inasmuch as we have not convinced ourselves of the negligibility of gross diffusion *versus* perfusion as a mechanism of uptake of cyclopropane in adipose tissue, the calculated results by the present perfusion-limited model are offered as valid only in order of magnitude. In particular, the derived rate of blood flow to the total body adipose tissue derived by neglecting gross diffusion is too high and consequently should be considered as an upper-limiting value.

Assumption (*b*): Concentrations of substance in blood can be related by appropriate partition coefficients to concentrations of substance in compartments. This assumption is applied in the following form. Blood leaving a compartment is assumed to be in solubility equilibrium with the average concentration of gas existing at that time in the tissues of the compartment. If this assumption is not valid, *i.e.*, if less cyclopropane is being transferred from blood to compartment than is given by using an equilibrium tissue-blood partition coefficient at the venous end of the compartment (owing to possible slowness of local diffusion relative to speed of blood flow through capillaries), then the primary error of the model will be to yield from the data too low values of the blood flow rates to the several body compartments.

Assumption (*c*): A steady physiological state exists, *i.e.*, all blood flow rates and solubility volumes are constant in time. Certain indications in the data of possible deviation from a steady physiological state will be pointed out later.

One other major simplification of the analysis is made. The alveolar volume should be treated as a separate body compartment in series with the external volume. However, it equilibrates with an external concentration of foreign gas so rapidly that this phase of body uptake can be regarded as essentially instantaneous in deriving quantities which depend on long times of uptake. Sechzer, Dripps, and Price (11) have observed experimentally that approximately 90 per cent of a constant external concentration of cyclopropane is reached in the alveolar volume in less than 10 min. Of primary interest in the present experiments are the "slowest" uptake half-times which were in the range 90 to 150 min. Moreover, preliminary calculation of the effect of the alveolar volume as a separate compartment, by using the formulation of Kety (7) but extended to the present multi-compartment model, indicates that the effect on the calculated blood flow rate to the "slowest" compartment is less than 5 per cent from this source. Therefore, the simplification of combining the lung volume with the external volume as a single "respiratory circuit volume" compartment appears permissible.

APPLICATION OF MODEL TO EXPERIMENT

The simplified model that emerges from the preceding considerations is the well-known closed n-compartment mammillary model in which a central compartment, here the respiratory circuit volume, exchanges with $n-1$ other compartments, which do not exchange with each other (12, 13). A general feature of compartment models, of which the details pertinent to the present case are given in Appendix A, is that the theoretical quantity which is identified with the experimentally measured quantity $q(t)$ is the sum of a number n of decay-type exponential functions of time. Accordingly, the experimental data (Figs. 1, 2) were examined as to the possibility of being curve-fitted by exponentials. They were found to be representable within experimental error by a constant (regarded as an exponential with rate constant zero) plus a minimum of three additional exponentials, as follows:

$$q(t) = q_\infty + a_1 e^{-k_1 t} + a_2 e^{-k_2 t} + a_3 e^{-k_3 t} \tag{3}$$

Thus, the first result yielded by application of the model is that a minimum of three distinct body compartments exists for the respiratory uptake of cyclopropane. Of the seven numbers q_∞, a_j, k_j ($j = 1, 2, 3$), which represent the results of an experiment, however, a_3 is not an independent number, having been derived to satisfy the theoretical model relationship for zero time (see Appendix B)

$$1 = q_\infty + a_1 + a_2 + a_3 \tag{4}$$

In addition, the fastest rate constant k_3 is considered unreliable and unusable because of scantiness of experimental data in the initial period in which this exponential makes its greatest contribution. Therefore, only five numbers are available in each experiment from which to derive *via* the model specific values characterizing the body compartments.

The parameters characterizing the four compartments of the model are eight in number, the four solubility volumes v_0, v_i ($i = 1,2,3$) and the four blood flow rates F, F_i ($i = 1,2,3$). Of these, $v_0 = \lambda_0 V_0$ is known from the experimental arrangement and the solubility properties of cyclopropane (see equations (A13), (A14)). The blood flow rate F is identified with the total cardiac output, which is estimated for each subject (see next section). Furthermore, F is equated to the sum $F_1 + F_2 + F_3$ of the blood flow rates to the body compartments, by the assumption that circulatory shunts across the lungs and tissues may be neglected. The number of unknown model parameters has now been reduced to five, namely, the three solubility volumes v_i ($i = 1,2,3$) and any two of the three blood flow rates F_i ($i = 1,2,3$). The mathematical relationships of the model connect the model parameters with the exponential parameters which represent the data. The five model parameters can be determined uniquely in terms of the five exponential parameters. Some details relevant to this determination are given in Appendices A, B. The results are given in the next section.

RESULTS

Basic Data. The basic data for the six normal subjects are given in Table I. The respiratory circuit volume V_0 was measured by a nitrogen dilution technique (2,3). The respiratory circuit solubility volume v_0 is defined in Appendix A, equations (A13), (A14) as $\lambda_0 V_0$ where $\lambda_0 \approx 2.3$ is approximately the reciprocal of the Bunsen solubility coefficient of cyclopropane in blood.[4] The estimated total

TABLE I

BASIC DATA FOR SIX NORMAL SUBJECTS

Subject, age, sex	Height H, cm	Weight W, kg	Respiratory circuit volume V_0, liter	Respiratory circuit solubility volume v_0, liter	Estimated total cardiac output F, liter/min.*	Total body fat W_f, kg†
VL, 19 ♀	160.7	52.40	19.6	45.6	5.16	13.9
GK, 38 ♀	155.6	53.30	21.0	48.5	5.07	10.7
TJ, 32 ♂	168.3	70.08	19.0	44.1	6.02	12.9
FK, 29 ♂	170.2	73.26	18.5	42.7	6.19	15.9
EB, 36 ♂	183.0	76.0	19.7	45.6	6.64	18.9
PD, 30 ♂	177.2	80.29	18.6	43.4	6.62	19.7

* $F = 3.35 \times 71.84 \times 10^{-4}$ (H, cm)$^{0.725}$ (W, kg)$^{0.425}$, see (15, 16).
† See (3).

cardiac output F was obtained by multiplying an assumed average cardiac index for the sitting position, 3.35 liters/min.M^2 (15), by the body surface area, M^2, calculated from height and weight by the DuBois formula (16). Total body fat, W_f, was calculated from the equilibrium uptake of cyclopropane as given by q_∞, Table II (see reference 3 and equations (C4), (C5) in Appendix C).

Exponential Parameters from Curve-Fitting Experimental Data. The experimental data were curve-fitted by exponential functions by a method apparently first used for this purpose by Greville (17) and described in detail elsewhere (4). In this method the quantity $q(t)$ is plotted against its negative time derivative, $-\dot{q}(t)$. In the present case $\dot{q}(t)$ was obtained as the slope of a smooth curve drawn "by eye" through the experimental data (the solid lines in Fig. 1, continued as the solid lines in Fig. 2). The linear appearance of the plot at large time (the square points of Fig. 2) indicated that a straight line (the dashed lines of Fig. 2) could fit the data adequately in this region. The q-axis intercept and the slope of this straight line are respectively the constant q_∞ and the reciprocal of the rate constant

[4] A Bunsen solubility coefficient of cyclopropane in blood of 0.40 ± 0.04 ml STP cyclopropane/ml blood at 37°C is used in this paper. This coefficient can be calculated additively from an assumed normal composition of blood, using measured solubility coefficients of cyclopropane in isosmotic saline and protein suspensions (1) and in fat (8). The calculated value compares well with the mean of measured solubility coefficients of cyclopropane in blood (14). The indicated uncertainty of ± 10 per cent is ascribed to variations in the plasma-cell ratio and in the lipid content of blood (14).

TABLE II

EXPONENTIAL PARAMETERS FROM CURVE-FITTING CYCLOPROPANE UPTAKE DATA BY $q\dot{q}$ METHOD

Subject	Equilibrium value, %	Amplitudes, %			Rate constants, min.$^{-1}$			Half-lives, min.		
	q_∞	a_1	a_2	a_3	k_1	k_2	k_3	T_1	T_2	T_3
VL ♀	9.75	33.8	28.3	28.2	0.00807	0.0328	0.108	85.9	21.1	6.42
GK ♀	12.60	37.2	28.7	21.5	0.00772	0.0487	0.146	89.8	14.2	4.74
TJ ♂	9.68	13.5	28.9	48.0	0.00400	0.0199	0.101	173	34.8	6.84
FK ♂	7.93	11.8	44.8	35.5	0.00363	0.0244	0.183	191	28.4	3.79
EB ♂	7.30	11.0	47.6	34.1	0.00466	0.0263	0.123	149	26.3	5.62
PD ♂	6.70	21.4	48.3	23.7	0.00527	0.0291	0.220	131	23.8	3.16

k_1 of the "slowest" exponential, equation (3). The exponential amplitude q_1 is obtained as the slope of the straight line portion of a plot of $q(t)$ *versus* $e^{-k_1 t}$. The exponential $q_1 e^{-k_1 t}$ is then subtracted from $q(t)$, and the process is repeated to give the parameters of a second, "faster" exponential $q_2 e^{-k_2 t}$ etc.

In each of the present experiments the method yielded, in addition to the constant q_∞, three exponentials as the minimum number required to fit the data within the experimental uncertainty (Table II). The reliability of the two most important exponential parameters, q_∞ and k_1, is indicated by the possible variations in drawing the straight (dashed) lines in Fig. 2. Two independent measures of reliability of the exponential parameters were available in two additional curve-fit solutions for each case.[5] The first was a least squares fit to the logarithm of the given unsmoothed data (the circles of Fig. 1). The second was a least squares fit to the logarithm of the smoothed data (values taken from the solid lines of Figs. 1 and 2). Detailed comparison between these solutions and the present solution is given for cases GK and EB in reference 4. From comparison among these solutions and from the graphical display yielded at all stages of the present method, the uncertainty of q_∞ was judged to be of the order of 5 per cent and that of the parameters of the two slower exponentials of the order of 20 per cent. As previously discussed, the fastest rate constant k_3 is not used to derive physiological results, and a_3 is used by way of a correction to results which depend primarily on the two slower exponentials.

Worthy of note are the differences between the results for the two female subjects and the four male subjects (Table II). The half-lives T_2 and especially T_1 are smaller, and the amplitude a_1 larger, for the females than for the males. Also the q *versus* $-\dot{q}$ plots (Fig. 2) seem more "oscillatory" for the females than for the males. Such "oscillations" may conceivably correspond to deviations from a steady internal state in the subject, perhaps due to shunting of blood flow from one type of body tissue to another during the course of the experiment (3).

[5] These solutions were kindly derived and supplied by Dr. Mones Berman, of the National Institutes of Health, using IBM punch card computers.

TABLE III

PHYSIOLOGICAL PARAMETERS OF MODEL DERIVED FROM EXPONENTIAL PARAMETERS OF EXPERIMENTAL DATA

Subject	Solubility volumes, liters			Blood flow rates, liters/min.			Half-life, min.
	v_1	v_2	v_3	F_1	F_2	F_3	T_{α_3}
VL ♀	386	20.4	15.6	0.61	0.46	4.10	1.93
GK ♀	301	23.9	11.5	0.54	0.79	3.74	1.70
TJ ♂	321	58.6	32.3	0.45	0.57	4.99	2.49
FK ♂	399	75.7	20.1	0.47	0.69	5.04	1.84
EB ♂	488	70.9	20.1	0.67	0.68	5.29	1.78
PD ♂	550	42.9	12.3	0.54	0.58	5.50	1.20

Physiological Parameters Derived from Exponential Parameters. With q_∞, a_1, a_2, k_1, k_2 (Table II), and v_0, F (Table I) as input data for the mathematical relationships of the model (Appendix A), the solubility volumes v_1, v_2, v_3, and blood flow rates F_1, F_2, F_3 were derived (Table III). An auxiliary quantity α_3 is also determined in this derivation. This quantity, see equation (A17), is the rate constant of the fastest exponential occurring in the model. It has only limited physical significance in that if the initial mixing and lung fill-up phenomena were negligible, and sufficient experimental data were available in the initial period to yield a reliable rate constant k_3 by curve-fitting, then this k_3 would equal α_3. For completeness and convenience in checking the calculations the derived values of α_3 are included in Table III as the half-times $T_{\alpha_3} = 0.693/\alpha_3$.

Particularly striking is the large value of v_1 in comparison with v_2 and v_3 and the approximately equal and low values of F_1 and F_2 in comparison with F_3. The first result, in view of the approximately 33 times greater solubility of cyclopropane in fat than in fat-free tissue indicates that compartment 1 must contain most of the body adipose tissue. Compartments 2 and 3 must therefore contain mostly fat-poor tissues. Since the blood flow rate F_3 is much greater than F_2, compartment 3 may be tentatively identified with highly perfused viscera and compartment 2 with lesser perfused non-adipose tissue such as resting muscle, skin, and connective tissue. A more detailed version of this argument is given in Appendix C. If this identification is not grossly in error the conclusion is indicated that, at rest, the body adipose tissue of a normal subject takes about as much of the total cardiac output as all the less well-perfused fat-poor tissue combined (such as resting muscle, skin, and connective tissue).

An important practical feature of the present experiment is the so-called speeding-up effect. The solubility volume perfusion $\phi_i = F_i/v_i$ has the physical significance, in the present perfusion-limited model, of being the rate constant of the ith exponential which can be curve-fitted to the uptake or elimination curve that would be obtained under conditions of constant external gas concentration (or infinite external volume). For compartment 1 the model solution (Table III)

yields a half-time $0.693/\phi_1$ in the range 400 to 700 min. On the other hand, the present experiment yielded a slowest observed half-time T_1 in the range 90 to 200 min. (Table II). A similar but lesser speeding-up effect exists for the "faster" half-times. Thus, the present perfusion-limited model shows that the smaller the respiratory circuit volume, the faster will equilibrium be approached. Consequently, a given period of experimental observation will yield a more complete record of the approach to equilibrium and will permit more accurate resolution of this record into exponentials, under small external volume conditions than under constant external concentration conditions.

Weight of Body Compartments. The weight of the three body compartments can be derived, and the fat to fat-free weight ratio of any one of them, if the fat to fat-free weight ratios of the other two are known or assumed. The solubility volume of a body compartment is essentially the product of the solubility coefficient of cyclopropane in that compartment and the weight of the compartment (Appendix C). The solubility coefficient can be determined from the known solubility coefficients of cyclopropane in fat and in fat-free lean mass if the fat to fat-free ratio is known. The solubility volume divided by this solubility coefficient then yields the weight of the compartment. Since the weights of all body compartments should add up to the known total body weight (if all parts of the body are represented in the experimental data in the manner described by the model), the fat to fat-free ratio need be known or assumed for only two compartments. The weight and fat to fat-free ratio for the remaining compartment can then be deduced.

This type of calculation is illustrated for subject EB in Table IV. It is seen that the fat ratio of compartment 2 goes down as the fat ratio of compartment 3 goes up and that the two are equal at approximately 3 per cent, a not unreasonable order of magnitude for lipid content of non-adipose tissues such as muscle and viscera (18). The assumption of 80 per cent rather than 60 per cent fat content for compartment 1 (probably largely adipose tissue) gives a greater fat-free weight in compartment 2. Too low an assumption of fat content in compartment 1 (below about 30 per cent) would produce negative values for fat-free weight in compartment 2.

The particular assumptions of 80 per cent fat content in compartment 1 and 3 per cent fat content in compartment 3 for normal humans are suggested by the work of Pitts (18) and others and were used to calculate compartment compositions for all the subjects (Table V). The results in all cases are qualitatively similar. The slightly negative values of W_{f2} for the two female subjects could be changed to positive values by assuming slightly less fat in the other compartments, in particular compartment 1. The results in Tables IV and V tend to support the qualitative interpretation of the anatomical nature of the three derived body compartments.

The nature of the changes in gross body composition as a result of loss or gain of body weight is of obvious physiologic interest. The preceding possibility resulting from the cyclopropane uptake experiment, of dividing up total body fat and total

fat-free body weight into portions assignable to anatomically distinct types of tissues, appears to be capable of yielding information relevant to this problem. Specifically, information as to the degree to which adipose and other tissues change in weight and in relative composition of fat to fat-free components for a given change in body weight, might be derived by applying the present model to precise gas uptake experiments on a given subject before and after weight change.

Perfusion of Body Compartments. It has been seen how blood flow rates and solubility volumes of the several body compartments can be derived (Table III) from the exponential parameters of the observed uptake curves. From

TABLE IV

COMPOSITION OF THE THREE BODY COMPARTMENTS FOR VARIOUS ASSUMED RELATIVE COMPOSITIONS OF COMPARTMENTS 1 AND 3

Subject EB♂, W = 76.0 kg, W_f = 18.9 kg, W_l = 57.1 kg

$\frac{W_{f1}}{W_1}$	W_{f1}	W_{l1}	$\frac{W_{f3}}{W_3}$	W_{f3}	W_{l3}	W_{f2}	W_{l2}	$\frac{W_{f2}}{W_2}$
1.0	17.3	0	0	0	24.3	1.6	32.7	.046
0.8	17.2	4.3	0	0	24.3	1.7	28.5	.056
0.6	17.0	11.3	0	0	24.3	1.9	21.5	.081
1.0	17.3	0	0.03	0.4	11.8	1.2	45.3	.026
0.8	17.2	4.3	0.03	0.4	11.8	1.3	41.0	.031
0.6	17.0	11.3	0.03	0.4	11.8	1.5	34.0	.042
1.0	17.3	0	0.06	0.5	7.7	1.1	49.4	.022
0.8	17.2	4.3	0.06	0.5	7.7	1.2	45.1	.026
0.6	17.0	11.3	0.06	0.5	7.7	1.4	38.1	.035
1.0	17.3	0	0.09	0.6	5.6	1.0	51.5	.019
0.8	17.2	4.3	0.09	0.6	5.6	1.1	47.2	.023
0.6	17.0	11.3	0.09	0.6	5.6	1.3	40.2	.031

Notation: W_i = weight, W_{fi} = fat weight, W_{li} = fat-free weight, of compartment i, $W_i = W_{fi} + W_{li}$.

TABLE V

COMPOSITION OF BODY COMPARTMENTS ASSUMING 80 PER CENT FAT IN COMPARTMENT 1 AND 3 PER CENT FAT IN COMPARTMENT 3. NOTATION AS IN TABLE IV

Subject	W_{f1}	W_{l1}	W_{f2}	W_{l2}	W_{f3}	W_{l3}	W_1	W_2	W_3
VL ♀	13.6	3.41	−0.04	25.9	0.28	9.17	17.0	25.9	9.5
GK ♀	10.6	2.65	−0.12	33.2	0.21	6.79	13.3	33.0	7.0
TJ ♂	11.3	2.83	1.05	35.3	0.59	19.0	14.1	36.3	19.6
FK ♂	14.1	3.52	1.46	41.9	0.37	11.9	17.6	43.4	12.2
EB ♂	17.2	4.31	1.32	40.9	0.37	11.8	21.5	42.2	12.2
PD ♂	19.4	4.85	0.11	48.5	0.22	7.26	24.2	48.6	7.5

the solubility volumes have been deduced weights of tissues constituting the compartments, with the aid of plausible assumptions for fat to non-fat ratio of two of the body compartments (Tables IV and V). One can now divide blood flow rate, F_i, by compartment weight, W_i, to obtain the ratio denoted as perfusion of the compartment (Table VI). For comparison, the average perfusion of the whole body, which is not derived from the model, *i.e.*, the estimated total cardiac output F divided by body weight W (Table I), is included in the last column of Table VI. The perfusion of compartment 1 is in the range 2 to 4 ml/min./100 gm. The perfusion of compartment 2 is about half that of compartment 1. The perfusion of compartment 3 is in the range 25 to 73 ml/min./100 gm.

TABLE VI

PERFUSION OF BODY COMPARTMENTS

Subject	$100\ F_1/W_1$*	$100\ F_2/W_2$* ml/min./100 gm	$100\ F_3/W_3$*	$100\ F/W$† ml/min./100 gm
VL ♀	3.6	1.8	43	9.9
GK ♀	4.1	2.4	53	9.5
TJ ♂	3.2	1.6	25	8.6
FK ♂	2.6	1.6	41	8.4
EB ♂	3.1	1.6	43	8.7
PD ♂	2.2	1.2	73	8.2
Mean	3.1	1.7	46	8.9

* From Tables III, V. † From Table I.

These values of perfusion are not incompatible with reported values. The range of values derived for compartment 3 agrees in order-of-magnitude with the values quoted for well-perfused viscera (16). The perfusion of compartment 2 may be compared with the values $3.0\ ^{+3.5}_{-0.7}$ ml/min./100 gm for resting muscle (16). Jones (5) has given the values 1 to 2.5 ml/min./100 ml for perfusion of resting muscle and the value 1.3 ml/min./100 ml for perfusion of adipose tissue. The muscle values were obtained as the rate constants of exponentials determined by curve-fitting nitrogen, krypton, and xenon elimination and uptake data. The experiments were done under conditions of constant external concentration in which the model analysis reduces to identifying each exponential with one compartment. The adipose tissue value was obtained as the slowest rate constant of a sum of five exponential functions fitted to a nitrogen elimination curve for the whole body. In a recent paper Lundin (19) has derived from a series of nitrogen elimination experiments at constant external concentration the range of values 4.6 to 6.1 ml/min./100 ml for perfusion of resting muscle and the range of values 2.4 to 4.0 ml/min./100 ml for perfusion of adipose tissue. These ranges were derived respectively from the two rate constants (half-times 12 to 15 min. and 90 to 150 min. respectively) into which the data could be resolved by exponential curve-fitting.

The values of perfusion derived in this paper are valid if the perfusion-limited model by which they were derived is valid. In particular, the values derived for the compartment interpreted as adipose tissue are estimated as about ±20 per cent uncertain, largely on account of uncertainty in estimating the slowest rate constant k_1 from the data. If, however, the model is in error because of appreciable gross diffusion of cyclopropane into adipose tissue from more quickly saturated neighboring tissue, then the present values of perfusion of adipose tissue are overestimated and should be regarded as of the nature of upper-limiting values.

The Course of Cyclopropane Uptake in Body Compartments. The kinetic aspects of uptake of fat-soluble inert substances are known to be fundamental to various problems of anesthesia. Recent kinetic considerations have been set forth by Price and co-workers (20, 21) and by Goldstein and Aronow (22) for the cases of thiopental and pentobarbital injected into the blood (which acts as the external volume of the present model) and the subsequent different rates of uptake by the several body tissues. Also, decompression sickness requires for its understanding a knowledge of the kinetics of distribution in the body of a fat-soluble inert gas (nitrogen) (5,23). It is therefore of interest to illustrate the kinetic results of the present model analysis by exhibiting the calculated time course of cyclopropane uptake in the several body compartments.

The fractional amount of cyclopropane $q_i(t)$ in each body compartment as a function of time is given by equations (A17), (A21), (A22). As an example, for subject EB,

$$\begin{aligned} q_1(t) &= 78.2 - 48.9\,e^{-k_1 t} - 28.0\,e^{-k_2 t} - 1.3\,e^{-\alpha_3 t} \\ q_2(t) &= 11.3 + 33.0\,e^{-k_1 t} - 42.9\,e^{-k_2 t} - 1.4\,e^{-\alpha_3 t} \\ q_3(t) &= 3.2 + 4.9\,e^{-k_1 t} + 23.3\,e^{-k_2 t} - 31.4\,e^{-\alpha_3 t} \end{aligned} \tag{5}$$

in which $q_i(t)$ is expressed in units of per cent, k_1, k_2 are given in Table II, and α_3 is obtained from Table III. These $q_i(t)$ are shown graphically (Fig. 4*a*), together with the smoothed experimental curve $q(t)$ for the respiratory circuit volume. The results may also be exhibited as the partial pressure of cyclopropane in each compartment as a function of time. This quantity, expressed as a fraction of the initial partial pressure of cyclopropane in the alveolar volume, is given by

$$P_i(t) = \frac{v_0}{v_i}\, q_i(t) \tag{6}$$

$P_i(t)$ is plotted in Fig. 4*b*, together with the experimental $q(t)$, which may also be regarded as the partial pressure in the external volume divided by the initial partial pressure in the external volume (after mixing with the alveolar gases). The quantities $q(t)$ and $P_i(t)$, $i = 1, 2, 3$, all approach the same value at $t = \infty$. The curves show among other things how the two fast compartments (2 and 3) fill up rapidly to the partial pressure of the external volume and then "join with" the external volume in "feeding" the adipose tissue compartment. This behavior of the three

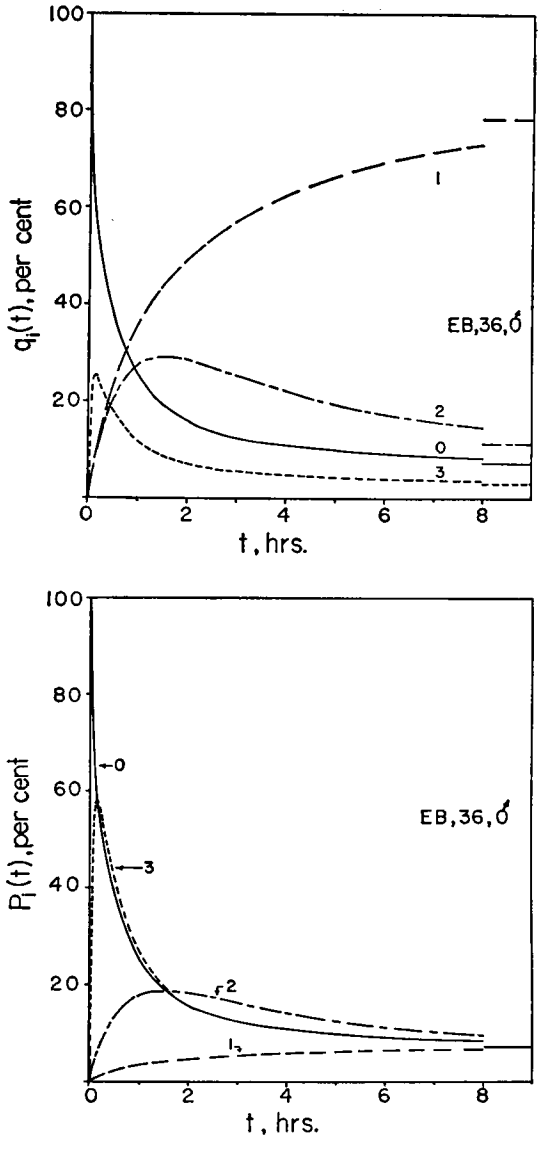

FIGURE 4*a* and *b* Time course of inert gas uptake by body compartments. Compartment numbers i indicated for each curve: $i = 0$, respiratory circuit volume; $i = 1$, 2, 3, body compartments. Horizontal lines at right of each curve are asymptotic values for $t \rightarrow \infty$.

(*a*) Ordinate: Amount of cyclopropane in compartment i at time t as percentage of total cyclopropane in system. Abscissa: time, t, hours.

(*b*) Ordinate: Partial pressure of cyclopropane in compartment i at time t as percentage of initial partial pressure of cyclopropane in respiratory circuit volume. Abscissa: time, t, hours.

body compartments is in sharp contrast to their course of uptake under the conditions of constant external concentration, in which case each compartment fills up to its equilibrium value independently of the others as a single exponential function of time.

CONCLUSIONS

1. The existing perfusion-limited model of inert gas exchange by the body is compatible with the present cyclopropane uptake experiments.
2. Analysis by this model of uptake data on six normal resting subjects yielded the following results:
   (*a*) The body is composed of three compartments, or cyclopropane spaces, which are anatomically compatible with (1) adipose tissue; (2) resting muscle, skin, and connective tissue; (3) highly perfused viscera.
   (*b*) The rates of blood flow to compartments 1 and 2 are approximately equal and are of the order of 10 per cent of the total cardiac output.
   (*c*) The rates of blood flow per unit compartment weight (perfusion) were in the following ranges: compartment 1, (adipose tissue), 2 to 4 ml/min./100 gm; compartment 2, (resting muscle, skin, etc.), 1 to 2.5 ml/min./100 gm; compartment 3, (highly perfused viscera), 25 to 75 ml/min./100 gm.
   (*d*) The time course of cyclopropane uptake in each body compartment is described by a constant plus three exponential functions of time.

   These results may be regarded as quantitative if the perfusion-limited model from which they were calculated proves valid. To the extent that tissue-to-tissue diffusion processes compete with perfusion processes, the quantitative significance of the results becomes more limited. At present the precise extent of such diffusion processes relating to adipose tissue is unknown.
3. Kinetic analysis of experiments on fat-soluble inert gas uptake would appear to be a useful tool in such problems as:
   (*a*) Gross body composition and its changes with body weight change.
   (*b*) rate of blood flow to total body adipose tissue and its variations under different conditions of the subject.
   (*c*) Narcotic action of fat-soluble anesthetics.
   (*d*) Decompression sickness.

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APPENDIX A

MATHEMATICAL TREATMENT OF MODEL

The model consists of a finite number of compartments connected in parallel *via* the blood circulation with a closed respiratory circuit of constant volume (Fig. 3). The total amount Q (moles) of cyclopropane in the system is constant and equal to the sum of the amounts $Q_i(t)$ in the various body compartments plus the amount $Q_0(t)$ in the respiratory circuit volume. In terms of the fractional amounts

$$q_\nu(t) = Q_\nu(t)/Q, \quad \nu = 0, 1, 2, 3 \tag{A1}$$

this condition is

$$q_0 + q_1 + q_2 + q_3 = 1 \tag{A2}$$

The average concentration $C_i(t)$ of cyclopropane in the ith body compartment is defined by

$$V_i C_i(t) = Q_i(t) \tag{A3}$$

The respiratory circuit volume is defined by an analogous equation

$$V_0 C_e(t) = Q_0(t) \tag{A4}$$

in which $C_e(t)$ is the average concentration of cyclopropane in the external volume, which is the part of the respiratory circuit volume, external to the subject, in which measurements were made.

The four time-dependent variables of the model are taken as $q_\nu(t)$, $\nu = 0, 1, 2, 3$. One equation connecting these variables is equation (A2). Three more can be obtained from the Fick principle of perfusion applied to each body compartment,

$$\frac{dQ_i}{dt} = F_i(C_a - C_{vi}), \quad i = 1, 2, 3 \tag{A5}$$

in which $C_a - C_{vi}$ is the arteriovenous difference of concentration of cyclopropane for the ith compartment at time t. The analogous Fick equation for the respiratory circuit volume is already included in the preceding formulation. It is obtainable from substitution of equation (A5) into the time derivative of equation (A2) and by using the equations of continuity of flow of cyclopropane on arterial and venous sides of the circulation respectively,

$$C_a F_1 + C_a F_2 + C_a F_3 = C_a F \tag{A6}$$

$$C_{v1} F_1 + C_{v2} F_2 + C_{v3} F_3 = C_v F \tag{A7}$$

In equations (A6), (A7), all circulatory shunts are neglected and the concentrations all correspond to the same time; *i.e.*, the circulatory time lags in the arterial and venous bloods between lungs and body tissues (of order 1 min. or less) are neglected relative to the uptake times of primary interest in this experiment (of order 30 to 200 min.). Hence the time dependence of all concentrations can be indicated as $C(t)$.

The arterial and venous concentrations of cyclopropane are next related to the concentrations existing in the compartments. By the assumption of solubility equilibrium between blood and tissue at the venous end of each compartment,

$$C_{vi}(t) = \frac{C_i(t)}{\lambda_i} = \frac{V_i C_i(t)}{v_i} = \frac{q_i(t)}{v_i} Q \tag{A8}$$

By the assumption of solubility equilibrium between arterial blood and the alveolar gases

$$C_a(t) = \frac{C_A(t)}{\lambda_A} = \frac{C_A(t)}{C_e(t)} \frac{C_e(t)}{\lambda_A} \tag{A9}$$

By the neglect of lung "fill-up" time, the lung volume is assumed to be in equilibrium contact with the external volume at all times. Hence the ratio $C_A(t)/C_e(t)$ is constant and equal to its value at $t = \infty$. This value is given (3) by,

$$\frac{C_A}{C_e} = \frac{80}{79} \frac{T_e}{T_A} \left(\frac{p_e - p_{vA}}{p_e - p_{ve}} \right) \tag{A10}$$

where T_e, P_e, P_{ve} are temperature, pressure, and water vapor pressure in the external volume, and T_A, P_{vA} are temperature and water vapor pressure in the alveolar volume. The temperature and pressure factors in equation (A10) are given by the elementary gas

laws while the factor 80/79 represents the respiratory quotient effect (24); *i.e.*, the increase in equilibrium concentration of an inert gas in the alveolar volume because the rate of emission of carbon dioxide into this volume is less than the rate of absorption of oxygen from it. Expressing the partition coefficient in equation (A9) in terms of the Bunsen solubility coefficient of cyclopropane in blood α_{bl}, by

$$\lambda_A = \frac{1}{\alpha_{bl}} \frac{273}{T_A} \tag{A11}$$

and substituting equations (A11), (A10), and (A4) into (A9) yields

$$C_a(t) = \frac{q_0(t)}{v_0} Q \tag{A12}$$

where

$$v_0 = \lambda_0 V_0 \tag{A13}$$

and

$$\lambda_0 = \frac{1}{\alpha_{bl}} \left(\frac{79}{80}\right)\left(\frac{273}{T_e}\right)\left(\frac{p_e - p_{ve}}{p_e - p_{eA}}\right) \tag{A14}$$

The quantity v_0 may be regarded as the solubility volume of the respiratory circuit (external volume plus lung volume). Substitution of equations (A12) and (A8) into (A5) yields the three additional equations desired

$$\frac{dq_i}{dt} = F_i\left(\frac{q_0}{v_0} - \frac{q_i}{v_i}\right), \quad i = 1, 2, 3. \tag{A15}$$

In terms of the turnover rates $f_i = F_i/v_0$, $\phi_i = F_i/v_i$, equation (A15) can be written

$$dq_i/dt = f_i q_0 - \phi_i q_i, \quad i = 1, 2, 3 \tag{A16}$$

equations (A2) and (A16) define the model mathematically. Under steady state conditions the turnover rates f_i, ϕ_i ($i = 1, 2, 3$) are constant in time. Then the equations are linear with constant coefficients and have a solution of the form

$$q_\nu(t) = q_{\nu\infty} + \Sigma_j b_{\nu j} e^{-\alpha_j t}, \quad \nu = 0, 1, 2, 3 \tag{A17}$$

where Σ_j denotes summation from $j = 1$ to 3.

The relations between the exponential parameters in equation (A17) and the turnover rates in equation (A16) may be obtained by the "old-fashioned" method of substituting equation (A17) into (A16) and (A2), equating coefficients of like exponentials, and using the initial conditions $q_0(0) = 1$, $q_i(0) = 0$ ($i = 1, 2, 3$). These relations may be exhibited in a more concise and convenient form by the Laplace transform method (13). By this method, the Laplace transform $\bar{q}_0(p)$ of $q_0(t)$ is obtained from equation (A17) in the form

$$\bar{q}_0(p) = \frac{q_{0\infty}}{p} + \Sigma_j \frac{b_{0j}}{p + \alpha_j} \tag{A18}$$

On the other hand $\bar{q}_0(p)$ is obtained from equations (A16) in the form

$$\frac{1}{p\bar{q}_0(p)} = 1 + \Sigma_j \frac{f_j}{p + \phi_j} \tag{A19}$$

By putting either expression for $\bar{q}_0(p)$ into the form of the other, the turnover rates can be expressed in terms of the exponential parameters or *vice versa*. From the Laplace transform of $q_i(t)$,

$$\bar{q}_i(p) = \frac{f_i}{p + \phi_i} \bar{q}_0(p), \quad i = 1, 2, 3 \tag{A20}$$

the exponential parameters of the body compartments can be expressed as

$$q_{i\infty} = \frac{f_i}{\phi_i} q_{0\infty} = \frac{v_i}{v_0} q_{0\infty}, \quad i = 1, 2, 3 \tag{A21}$$

$$b_{ij} = \frac{f_i b_{0j}}{\phi_i - \alpha_j}, \quad i, j = 1, 2, 3 \tag{A22}$$

From equations (A21) and (A2) it follows in particular that

$$q_{0\infty} = \frac{v_0}{v_0 + v_1 + v_2 + v_3} \tag{A23}$$

In the present paper the turnover rates were first obtained from the exponential parameters by an iteration method based on the "old-fashioned" approach. The results were then checked by the Laplace transform method.

APPENDIX B

APPLICATION OF MODEL TO EXPERIMENT

In applying the model to the experiment to derive physical conclusions, various theoretical quantities of the model must first be identified with those quantities which can be considered as "actually measured." The actually measured quantities are, first, $C_c'(t)$, the concentration of cyclopropane (moles/liter) in the external volume at time t; second, $Q(t)$, the amount of cyclopropane (moles) initially introduced into the external volume minus the amount subtracted up to time t in sampling; and third, a constant volume V_N (liters), measured by a nitrogen dilution technique (2). The volume V_N comprises the external volume plus an effective lung volume such that the product $V_N C_c'(\infty)$ is the amount of cyclopropane in the external volume plus actual lung volume at sufficiently long time, when the lung volume is in "equilibrium contact" with the external volume. From the preceding actually measured quantities a derived experimental quantity is constructed to represent the data,

$$q(t) = \frac{V_N C_c'(t)}{Q(t)} \tag{B1}$$

The following identifications are now made: $C_c'(t)$ with the model quantity $C_c(t)$, equation (A4); V_N with the model quantity V_0, equation (A4); $Q(t)$ with the constant Q of the model, equation (A1); and $q(t)$ with the model quantity $q_0(t)$, equation (A1) with $v = 0$.

By the identification of $Q(t)$ with Q a sampling error is made. In the experiments less than 8 per cent of the amount added initially was removed for chemical analysis during the entire experiment of about 8 hrs. duration. Of this amount, about one-third was removed in the last 4 hrs. By using the variable $Q(t)$ in equation (B1) instead of, for example, the constant initial amount $Q(0)$, an attempt is made to allow partially for this error. Thus the sampling error, while difficult to assess quantitatively, should be no more than a few per cent.

The identification of $q(t)$, equation (B1), with the model quantity $q_0(t)$ is not made for the time range 0 to ∞. The first and last experimental measurements of $C_4'(t)$ were made some 12 minutes and 480 minutes after injection of cyclopropane into the external volume. Hence $q(t)$ can be identified with $q_0(t)$ only in the time range 12 min. to 480 min. In this time range the five numbers q_∞, a_1, a_2, k_1, k_2 are derived by curve-fitting exponential functions to $q(t)$. These numbers are derived experimental quantities in the same sense as $q(t)$, equation (B1), is derived from actually measured quantities. They are identified with the model quantities $q_{0\infty}$, b_{01}, $b_{0\infty}$, α_1, α_2 of equation (A17) with $\nu = 0$. Since these model quantities are functions of the model parameters v_0, v_4, F, F_4, this identification yields five relations from which five model parameters can be determined if the others are known or assumed.

The model was set up as a closed 4-compartment model, *i.e.*, as a constant plus three exponential model. The five numbers q_∞, a_j, k_j ($j = 1, 2$) which represent the data correspond, however, to a constant plus two exponentials. The reason for assuming the extra exponential in formulating the model was that the sum $q_\infty + a_1 + a_2$ obtained in the curve-fitting process was sufficiently less than one to warrant the assumption that another exponential existed having the model interpretation of an additional body compartment and satisfying the condition $q_\infty + a_1 + a_2 + a_3 = 1$ required by equation (A17) with $\nu = 0$, $t = 0$ (and identifying a_3 with $b_{0\infty}$). This assumption is expected to result in more accurate values of the model parameters v_1, v_2, F_1, F_2, which depend primarily on a_1, a_2, k_1, k_2, than the alternative procedure of using a closed 3-compartment model and representing the experimental results by a constant plus two exponentials with altered values a_1' and a_2' such that $q_\infty + a_1' + a_2' = 1$ (this alteration could be produced by changing the time scale by the substitution $t = t' + \delta$ and regarding t' as the physically correct time interval from the time zero of the experiment). The derived value of v_3, which depends primarily on a_3, is not expected to have much quantitative significance.

APPENDIX C

COMPOSITION OF BODY COMPARTMENTS

Consider first the whole body as composed additively of a weight of fat W_f, having a solubility volume $\lambda_f V_f$, and a fat-free lean weight W_l, having a solubility volume $\lambda_l V_l$. Then the total solubility volume of the body is given by (see equation (A23)),

$$\lambda_f V_f + \lambda_l V_l = v_1 + v_2 + v_3 = \left(\frac{1 - q_\infty}{q_\infty}\right) v_0 \tag{C1}$$

The partition coefficients λ_f, λ_l are given by the ratios

$$\lambda_f = \frac{\alpha_f}{\alpha_{bl}}, \quad \lambda_l = \frac{\alpha_l}{\alpha_{bl}} \tag{C2}$$

where α_f, α_l, α_{bl} are the Bunsen solubility coefficients of cyclopropane per unit volume of fat, fat-free lean mass, and blood respectively (ml STP/ml). In terms of the solubility coefficients α_f', α_l' per unit weight of fat and fat-free lean mass (ml STP/gm, see (1, 8)), defined by

$$\alpha_f V_f = \alpha_f' W_f, \quad \alpha_l V_l = \alpha_l' W_l \tag{C3}$$

equation (C1) becomes

$$\begin{aligned} \alpha_f' W_f + \alpha_l' W_l &= \alpha_{bl}(v_1 + v_2 + v_3) \\ &= \alpha_{bl} v_0 \left(\frac{1 - q_\infty}{q_\infty} \right) \end{aligned} \tag{C4}$$

The second form of equation (C4), combined with the body weight equation

$$W_f + W_l = W \tag{C5}$$

has previously been used (3) to calculate total body fat W_f and total fat-free lean mass W_l. To make inferences concerning the composition of the ith compartment as between fat W_{fi} and fat-free weight W_{li}, the equation analogous to the first form of equation (C4) is used.

$$\alpha_f' W_{fi} + \alpha_l' W_{li} = \alpha_{bl} v_i, \quad i = 1, 2, 3 \tag{C6}$$

As an example, for subject EB, Table III, and with the solubility coefficients (1, 3, 8), $\alpha_f' = 11.26$, $\alpha_l' = 0.33$, $\alpha_{bl} = 0.40$, equations (C6) are

$$11.26\ W_{f1} + 0.33\ W_{l1} = 195.4, \quad (F_1 = 0.67 \text{ liter/min.}) \tag{C7}$$

$$11.26\ W_{f2} + 0.33\ W_{l2} = 28.4, \quad (F_2 = 0.68 \text{ liter/min.}) \tag{C8}$$

$$11.26\ W_{f3} + 0.33\ W_{l3} = 8.03, \quad (F_3 = 5.29 \text{ liter/min.}) \tag{C9}$$

in which the corresponding blood flow rates to the respective body compartments (Table III) have been indicated on the right. The total body fat W_f and fat-free lean mass W_l can be expressed additively in terms of values for the three body compartments as

$$W_{f1} + W_{f2} + W_{f3} = 18.9 \text{ kg} \tag{C10}$$

$$W_{l1} + W_{l2} + W_{l3} = 57.1 \text{ kg} \tag{C11}$$

Since the sum of equations (C7 to C9) is equation (C4) which has been used in deriving equations (C10), (C11), only four of the five preceding equations are independent. Consider the four independent equations to be equations (C7), (C9), (C10), (C11). There are six unknowns, W_{fi}, W_{li} $(i = 1, 2, 3)$. Hence, two more conditions are needed. These are taken as

$$W_{f1} = x_1(W_{f1} + W_{l1}) \tag{C12}$$

$$W_{f3} = x_3(W_{f3} + W_{l3}) \tag{C13}$$

For given x_1, equations (C7), (C12) can be solved for W_{f1}, W_{l1}. For given x_3 equations (C9), (C13) can be solved for W_{f3}, W_{l3}. Then equations (C10), (C11) can be solved for W_{f2}, W_{l2} respectively. The results for subject EB are shown in Table IV.

The qualitative nature of the three compartments, which indicates the x_1, x_3 range of interest, is suggested by equations (C7), (C9), and the corresponding blood flow rates. Consider first equation (C7), corresponding to compartment 1. The right hand sides of equations (C7) to (C9) are proportional to the amounts of cyclopropane in the respective compartments. If the entire 57.1 kg of fat-free lean mass of the body were in compartment 1, only $0.33 \times 100 \times 57.1/195.4 = 9.7$ per cent of the cyclopropane in this compartment would be accounted for. The remainder, 90.3 per cent, requires $W_{f1} = 0.903 \times 195.4/11.26 = 15.7$ kg of fat to be present, which is 83.0 per cent of the total body fat. Such a combination of W_{f1} and W_{l1}, however, which amounts to almost the entire body, is anatomically incompatible with the derived blood flow rate of 0.67

liter/min. to this compartment. The composition of compartment 1 becomes compatible with its derived blood flow rate if W_{l1} is decreased substantially and W_{f1} increased slightly.

Consider, next, equation (C9) corresponding to compartment 3. If this compartment contained all fat and no fat-free lean mass, the entire cyclopropane content of the compartment would be accounted for by a fat content of $W_{f3} = 8.03/11.26 = 0.71$ kg. Such a combination of W_{f3} and W_{l3}, a very small proportion of the body, is anatomically incompatible with the derived blood flow rate of 5.29 liter/min. to this compartment. The composition of compartment 3 becomes compatible with its derived blood flow rate if W_{f3} is reduced to slight proportions and W_{l3} is increased substantially.

EXPLANATION OF IMPORTANT SYMBOLS

a_j = amplitude exponential parameter representing experimental data
$b_{\nu j}$ = amplitude coefficient of exponential in model solution
$C(t)$ = concentration of cyclopropane at time t, moles/liter
$C_e'(t)$ = experimentally measured concentration of cyclopropane in external volume
F = rate of blood flow, liters/minute
f_i = F_i/v_0, rate of blood flow per unit respiratory circuit solubility volume, minute^{-1}
k_j = rate constant exponential parameter representing experimental data, minute^{-1}
$P_i(t)$ = fractional partial pressure of cyclopropane in ith body compartment at time t
p = Laplace transform complex frequency variable
Q = constant total amount of cyclopropane in system in model, moles
$Q(t)$ = total amount of cyclopropane in system at time t in experiment, moles
$Q_\nu(t)$ = amount of cyclopropane in νth model compartment, moles
$q(t)$ = experimentally derived ratio of amount of cyclopropane in respiratory circuit volume to total amount of cyclopropane in system at time t
$\dot{q}(t)$ = dq/dt, time derivative of $q(t)$
$q_\nu(t)$ = $Q_\nu(t)/Q$, fractional amount of cyclopropane in νth model compartment
$q_\nu(p)$ = Laplace transform of $q_\nu(t)$
q_∞ = constant equilibrium value of $q(t)$ at $t = \infty$
$q_{\nu\infty}$ = constant equilibrium value of $q_\nu(t)$ at $t = \infty$
T_j = $0.693/k_j$, half-time of exponential representing experimental data, minutes
$T_{\alpha s}$ = $0.693/\alpha_s$, half-time derived in model analysis, minutes
t = time, minutes
V = volume, liters
V_R = experimentally determined respiratory circuit volume, liters
v = λV, solubility volume, liters
W = weight, kilograms
α = Bunsen solubility coefficient of cyclopropane, milliliters STP/milliliter
α' = Bunsen solubility coefficient divided by density, milliliters STP/gram
α_j = rate constant of exponential occurring in model analysis
λ = α/α_{bl}, partition coefficient of cyclopropane
ϕ_i = F_i/v_i, solubility volume perfusion, minute^{-1}

Subscripts

i = 1, 2, 3, body compartment
0 = respiratory circuit volume
ν = 0, 1, 2, 3, either respiratory circuit volume or body compartment
j = 1, 2, 3
A = alveolar volume
e = external volume
f = fat (lipid)
l = fat-free tissue (lean)
fi = fat in ith body compartment
li = fat-free tissue in ith body compartment
bl = blood