

Interactions among Ventilation, the Circulation, and the Uptake and Distribution of Halothane— Use of a Hybrid Computer Multiple Model:

I. The Basic Model

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The authors describe an 18-compartment hybrid computer multiple model of the uptake and distribution of halothane. This model uses 88 equations and 124 parameter settings. Three submodels are incorporated into the basic model: 1) The mass transport of halothane is simulated on the digital portion of the hybrid computer. 2) A breath-by-breath pulmonary model with two compartments describes air pressure-flow relations in the airway system. 3) A beat-to-beat cardiovascular model with 15 compartments describes in detail blood pressure-flow relations. In addition, a baroreceptor-heart rate loop is included: an increase in arterial pressure causes a decrease in heart rate. The slope of the baroreceptor response is progressively decreased by halothane until at 2 per cent there is no response.

The model of halothane uptake and distribution is separate from the blood and air pressure-flow models, but is, in effect, driven by them. Myocardial "contractility" (stroke volume) and certain regional vascular resistances can be affected by the concentration of halothane in one or any proportion of any combination of three compartments: arterial blood (arteriolar concentration), cerebral gray matter, or myocardial. In turn, these factors significantly affect the uptake and distribution of halothane.

The responses to three steady-state concentrations, as well as to a step change in concentration from 0 to 2 per cent, were examined. Twenty-four outputs were recorded, including halothane concentrations in ten compartments; myocardial "contractility"; left and right ventricular and right atrial pressures; cardiac output; stroke volume, R-R interval; and blood flows in six regions. Two variables—alveolar concentration of halothane and arterial blood pressure—were recorded during a step change of 0 to 5 per cent.

The model describes the appropriate steady-state and dynamic cardiovascular responses to halothane. It also demonstrates the complex interrelationships among cardiac output, regional blood flow distribution, and the uptake and distribution of halothane. During step changes in halothane concentration, most of the responses occur early, a phenomenon also seen in man and goats.

Thus, the model is useful not only for representing organ and tissue halothane concentrations, but also for gaining new insights into cardiovascular alterations produced by rapidly changing concentrations of halothane and into the complex interactions between the circulation and the uptake and distribution of halothane. (Key words: Anesthetics, volatile: halothane. Equipment, Computers. Pharmacokinetics: distribution; models; uptake.)

MODELS OF THE UPTAKE and distribution of anesthetic agents have been useful for several purposes: improving clinical care, teaching, helping to predict the actions of new anesthetic agents, suggesting optimal physical constants of agents yet to be synthesized, and testing automatic control systems for the administration of the drugs. Many models have been designed, most of them single and linear.¹⁻¹⁰ In a linear model, cardiac output and its distribution to the different regions of the body are assumed to be constant during the uptake of the anesthetic agent. However, anesthetic agents do influence the circulatory system. In turn, circulatory changes significantly affect the uptake and the distribution of the agents. Based on these facts, Smith and Zwart and their colleagues developed a nonlinear analog computer multiple model of the uptake and distribution of halothane.^{11,12} In this model, changes in cardiac output and its distribution were interdependently related to halothane concentration. The decrease in cardiac output was assumed to be a linear function of halothane concentration, and mean arterial blood pressure was obtained by dividing cardiac output by the total systemic conductance (inverse of resistance). The linear relation between cardiac output and halothane concentration, however, is doubtful.¹³ Moreover, the derivation of arterial blood pressure from cardiac output and its distribution was an oversimplification. Changes in halothane concentration affect the baroreceptor-heart rate relation, myocardial contractility, regional systemic vascular resistances, and other cardiovascular variables. Changes in these variables cause changes in heart rate, stroke volume, cardiac output, blood pressure, regional blood flow distribution, and venous return. There exist complex interdependent mechanisms between

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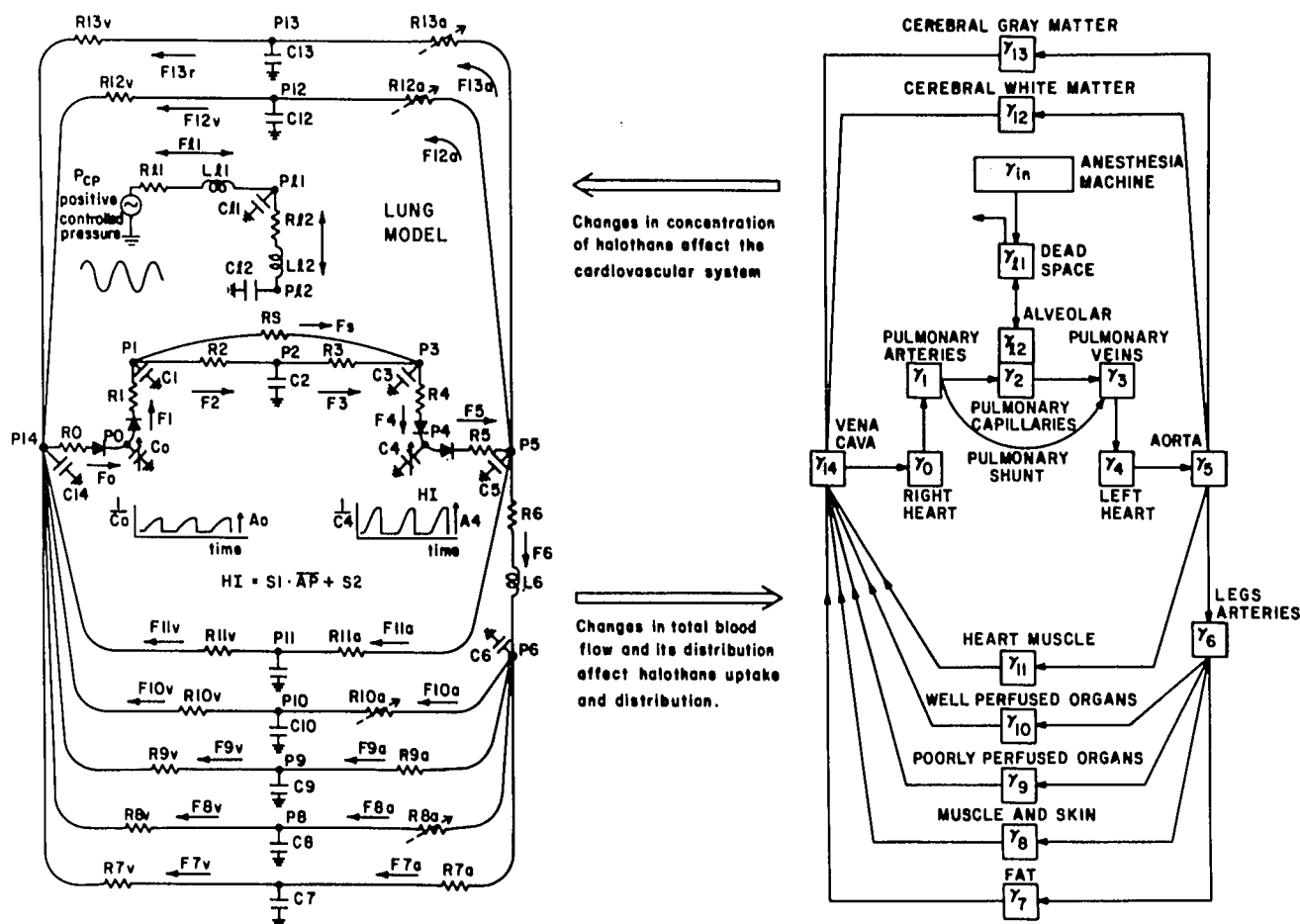


FIG. 1. Generalized scheme of the multiple model. *Right*, the 18-compartment model for the uptake and distribution of halothane. *Left*, the pulmonary (two segments) and cardiovascular (15 segments) models in electrical circuit form. The open arrows between the submodels indicate the interactions. The halothane concentration in one compartment or a combination of three compartments (arterial blood, cerebral gray matter, and/or heart muscle) affects several cardiovascular parameters: 1) the slope (S_1) and set value (S_2) of the baroreceptor response, 2) amplitudes (A_4 and A_0) for the reciprocal compliances of left and right ventricles, and 3) regional vascular resistances, as indicated by the dashed arrows. The changes in cardiovascular variables cause changes in the total blood flow and its distribution. In turn, these changes affect the uptake and distribution of halothane. The solid arrows in the lung/cardiovascular model represent the flow of air or blood, the latter out of the left heart, into the aorta, thence into the regional arteries, the veins, the vena cava, and right heart. R_s and F_s represent the right-to-left shunt, which is adjustable or controllable.

n = halothane concentration in vol per cent in n th compartment for the uptake and distribution model

P_n = blood or air pressure in n th segment

F_n = blood or air flow in n th segment

R_n = viscous flow resistance for n th segment (resistors)

L_n = fluid inductance for n th segment (inductors)

C_n = vessel or airway wall compliance for n th segment (capacitors)

HI = heart interval

S_1 and S_2 = the slope and the set value of the baroreceptor response

A_0 and A_4 = the amplitudes of reciprocal compliances for the right and left ventricles

the changes in these variables. To incorporate these facts, we developed a large hybrid computer[‡] multiple model of the uptake and distribution of halothane.

[‡] A hybrid computer is a combination of a digital computer and an analog computer.

Methods and Materials

The basis of the model is the multiple-modeling scheme.¹⁴ A multiple model, as the name implies, consists of more than one submodel, or circuit. Each of the submodels is complete in itself and could operate

independently, but in a multiple model each interacts with the others. Three submodels are incorporated into our basic model: a model of halothane uptake and distribution, a pulmonary model, and a cardiovascular model.

HALOTHANE UPTAKE AND DISTRIBUTION MODEL

The uptake and distribution of halothane is described by a mass-transport model which is simulated on the digital portion of the hybrid computer and which consists of 18 compartments, including the anesthesia machine, two pulmonary compartments, and 15 cardiovascular compartments, as shown on the right of figure 1. The latter 15 include: vena cava; right and left heart (one each); pulmonary blood (three), including a pulmonary shunt; arterial blood (two); muscle and skin; fat; and cerebral gray and white matter (one each). The values for the partition coefficients of halothane in the various compartments, as well as the initial (awake) blood flows to these compartments, have been listed in other publications.^{11,12} The two pulmonary compartments are dead space and alveolar. Several assumptions are made for the basic uptake and distribution model: (1) alveolar ventilation and the pulmonary right-to-left shunt are constant, (2) each of the compartments represents a perfect mixing chamber with instantaneous equilibration, (3) metabolism and cutaneous loss of halothane can be neglected, (4) there is no diffusion of halothane from well-perfused organs and muscle into fat, (5) there is no effect of CO₂ on the uptake and distribution of halothane, and (6) adaptation to the cardiovascular depressant effects of halothane does not take place. With these assumptions, 21 equations describing halothane exchange between different compartments have been set up and are available in archives.§

PULMONARY MODEL

A breath-by-breath model describes air pressure-flow relations in the airway system, as shown in the top left of figure 1. This is represented in a circuit form, which is a combination of viscous flow resistance, R; fluid inertance, L; and wall compliance, C. The

six equations representing pressure-flow relations are on deposit in archives.§

Since the basic model is intended to operate with controlled ventilation, we varied positive pressure applied to the lung airway model sinusoidally at constant frequency and amplitude to give constant respiratory rate and tidal volume (see fig. 1, upper left).

CARDIOVASCULAR MODEL

A beat-to-beat cardiovascular model describes blood pressure-flow relations, as shown in circuit form in the left of figure 1. Each segment in the cardiovascular system corresponds to a compartment in the halothane uptake and distribution model. Fifty-two equations represent the blood pressure-flow relations in the cardiovascular model. Cardiac contraction, in this model, is represented by time-varying compliances, one each for the left and right ventricles. The reciprocal compliance of the left heart has a larger amplitude than does that of the right heart, but has the same frequency and waveshape. The frequency of the time-varying reciprocal compliances for the ventricles, which is the heart rate, is influenced by the baroreceptor-heart rate control loop. A linear relation between mean arterial blood pressure and heart interval is assumed in this model, as described by

$$HI = \frac{1}{HR} = S_1 \bar{AP} + S_2$$

where HI = heart interval (electrocardiographic R-R interval); HR = heart rate; \bar{AP} = mean arterial pressure, which is chosen as the average pressure of P₃ in the model (fig. 1); S₁ = the slope in the relation between HI and \bar{AP} ; S₂ = the set value in the relation between HI and \bar{AP} . In this cardiovascular model, several cardiovascular parameters are affected by changes in concentration of halothane:

1) The slope (S₁) and set value (S₂) of the baroreceptor response are functions of halothane concentration in the cerebral gray matter compartment as described by

$$S_1 = S_1(0)\{1 + \alpha_1 \gamma_{13}\}$$

$$S_2 = S_2(0)\{1 + \alpha_1 \gamma_{13}\}$$

where S₁(0) = the slope of the baroreceptor-heart rate response before anesthesia and S₂(0) = the set point of the baroreceptor-heart rate response before anesthesia. γ_{13} = halothane concentration of the cerebral gray matter compartment. The slope is linearly decreased as a function of halothane concentration until at a 2 per cent concentration in gray matter there is no response (Smith NT, Fukui Y, unpublished observations).

§ See NAPS Document No. 03798 for 12 pages of supplementary material. Order from ASIS/NAPS c/o Microfiche Publications, P. O. Box 3513, Grand Central Station, New York, NY 10017. Remit in advance for each NAPS accession number. Institutions and organizations may use purchase orders when ordering; however, there is a billing charge for this service. Make checks payable to Microfiche Publications. Photocopies are \$5.00. Microfiche are \$3.00 each. Outside the United States and Canada, postage is \$3.00 for a photocopy or \$1.00 for a fiche.

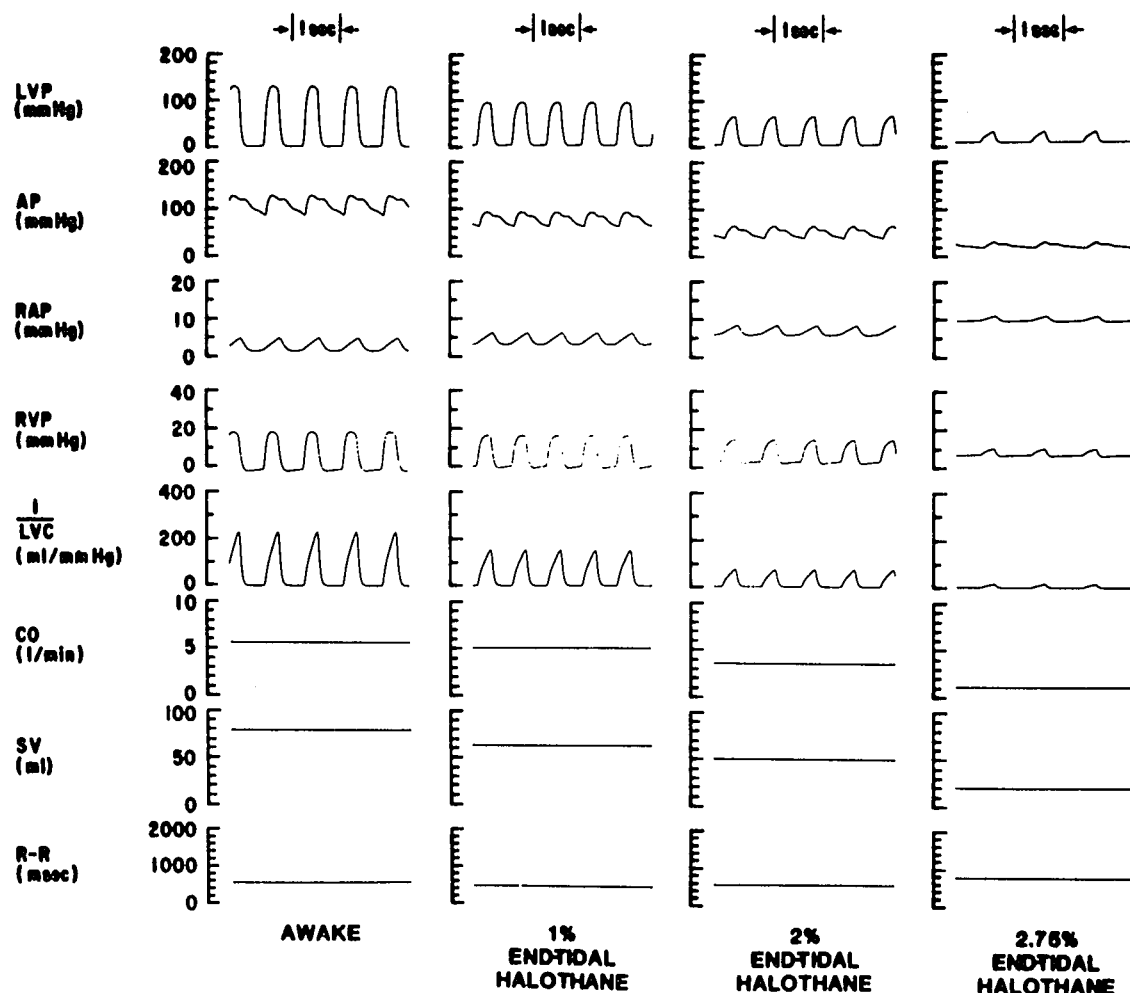


FIG. 2. Tracings of some cardiovascular variables during the awake state and at 1.0, 2.0, and 2.75 per cent end-tidal halothane concentrations equilibrated with all tissues and organs. LVP = left ventricular pressure; AP = arterial pressure; RAP = right atrial pressure; RVP = right ventricular pressure; $1/LVC$ = reciprocal of left ventricular compliance = "myocardial contractility" of left ventricle; CO = cardiac output; SV = stroke volume; R-R = electrocardiographic R-R interval.

2) The amplitudes of the reciprocals of heart compliances, which are related to myocardial "contractility" and to stroke volume, can be programmed to decrease as a function of halothane concentration¹⁷ in one of three compartments—arterial blood, gray matter of the brain, and heart muscle—or any combination of the three. The relations are

Amplitude of reciprocal compliance for left heart

$$= A_4 = A_4(0)\{1 + a_4\gamma^*\}$$

Amplitude of reciprocal compliance for right heart

$$= A_0 = A_0(0)\{1 + a_0\gamma^*\}$$

where $A_4(0)$ and $A_0(0)$ = the amplitudes of reciprocal compliances for the left and right ventricles prior to anesthesia; a_4 and a_0 = constants; γ^* = halothane concentration in one or any combination of arterial blood, gray matter of the brain, and heart muscle.

3) Certain regional vascular resistances, such as those in the muscle and skin, well-perfused organs, and cerebral gray and white matter compartments, decrease linearly as a function of halothane concentration in the arterial blood, that is, vasodilation occurs.^{11,12,15} Their equations are available in archives. §

The model was programmed on the hybrid computer facility of the Department of Electrical and Computer Engineering, University of Wisconsin. The time scale factor was 0.1, that is, the model operated at ten times real time. One hundred and twenty-four parameter settings were used in the model. These parameters have been taken and/or calculated from several references^{11-13,15-20} (fig. 2 gives one of the variables that have been programmed into the computer and whose values are modulated directly by the concentration of halothane: the inverse of left ventricular compliance ["contractility"]).

The cardiovascular and lung models were represented in the analog section (AD 256) of the hybrid computer, and halothane uptake and distribution in the digital section (SDS 930). The interconnections between the submodels were represented partly in the analog section and partly in the digital section.

Results

Figures 2–8 illustrate some of the outputs of the model. In figures 2 and 3 several cardiovascular variables are presented during the awake state and at 1.0, 2.0 and 2.75 per cent steady-state end-tidal halothane concentrations. These values assume that all compartments are saturated. Increases in halothane concentration reduce left and right ventricular systolic pressures, arterial pressure, the reciprocal of left ventricular compliance (myocardial "contractility"), cardiac output, and stroke volume, while increasing mean right atrial pressure. The R–R interval is reduced below the awake level at 2.75 per cent end-tidal halothane. Therefore, the reductions in cardiac output, which is the product of stroke volume and heart rate, at 1 and 2 per cent end-tidal halothane concentrations are primarily the result of changes in stroke volume. Blood flows, except that to cerebral

gray matter, decrease as end-tidal halothane concentration increases (fig. 3). Blood flows to the poorly perfused organs, fat, and heart muscle decrease 50 per cent at 2 per cent halothane. This is primarily the result of a 50 per cent reduction in arterial pressure. The 25 per cent reductions in blood flows to muscle and skin and the 22 per cent reduction in flows to well-perfused organs at 2 per cent halothane reflect partial counteraction of the reduction in arterial blood pressure by the vasodilating effect of halothane. The effects of profound vasodilation are particularly evident for cerebral blood flow. Cerebral blood flow increases at 1.0 and 2.0 per cent halothane, in spite of a moderate reduction in perfusing pressure, but reverts to less than the awake level at 2.75 per cent halothane when arterial pressure becomes extremely low.

The changes in compartmental halothane concentrations after a step change (0 → 2 per cent) in inspired halothane concentration are illustrated in figure 4, where myocardial compliance ("contractility") is controlled by the cerebral halothane concentration. Alveolar concentration is represented by the thick dotted line, which arises from respiratory fluctuations. The concentration in arterial blood closely follows the alveolar concentration. The response of halothane concentration in the gray matter of the brain is slower

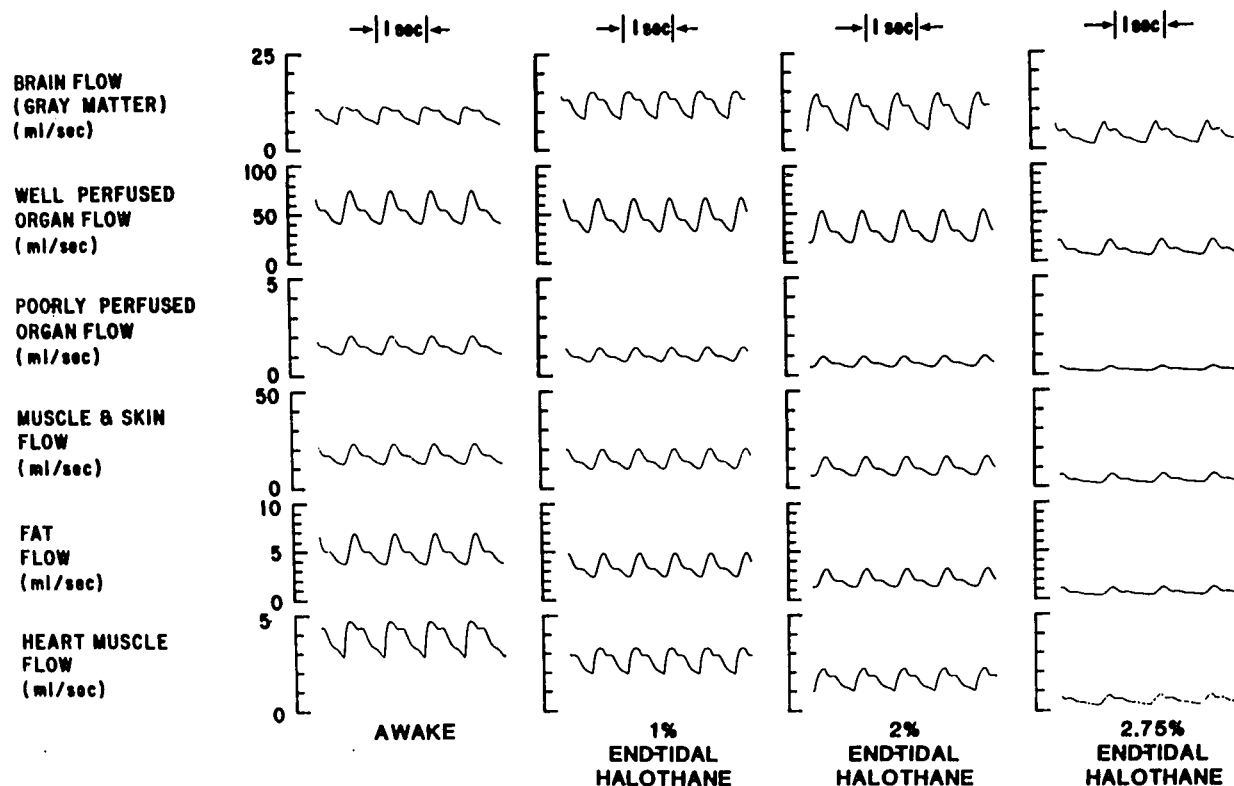


FIG. 3. Regional (compartmental) blood flows during the awake state and at equilibrated 1.0, 2.0 and 2.75 per cent end-tidal concentrations. Notice the variable effects of halothane on regional blood flows.

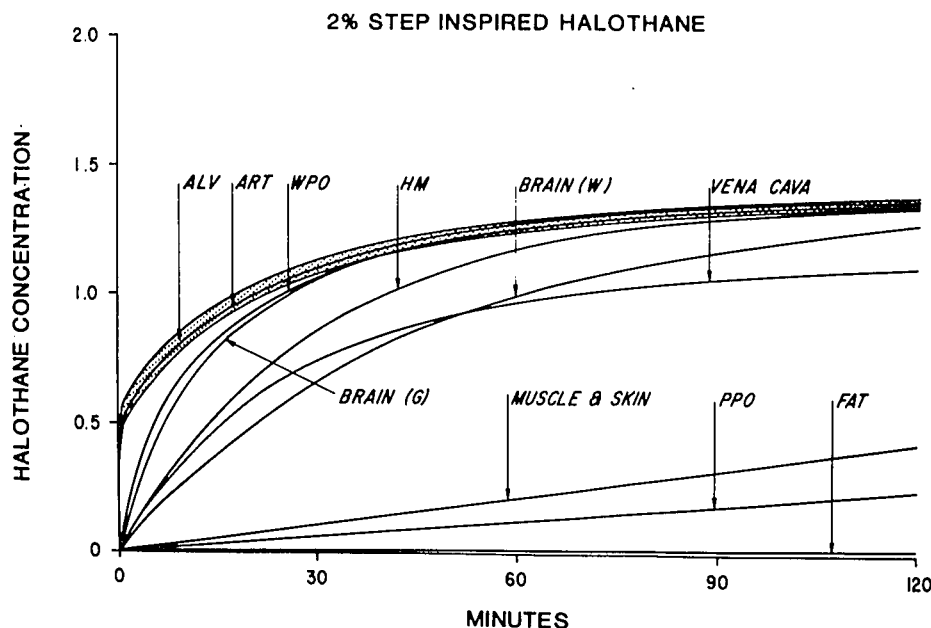


FIG. 4. Compartmental uptakes following a 0 \rightarrow 2 per cent step in inspired halothane. Myocardial compliance is controlled by the halothane concentration in the cerebral gray matter. ALV = alveolar; ART = arterial; WPO = well-perfused organs; HM = heart muscle; W = white; G = gray; PPO = poorly perfused organs. The thick dotted line represents respiratory variations in alveolar concentration.

than responses in arterial blood and the well-perfused organs, but faster than that in heart muscle. Halothane uptakes into the remaining compartments—cerebral white matter, muscle and skin, poorly perfused organs, and fat—are the slowest. Figure 5 depicts several cardiovascular responses to the same step change (0 \rightarrow 2 per cent) in inspired halothane concentration. Left and right ventricular systolic pressures, as well as arterial pressure, decrease with time, while right atrial pressure increases. Most of the changes in these pressures occur within the first 15 min after the step change of halothane. Of special interest in the response of the R-R interval, which initially decreases, then gradually increases back toward the awake level. The initial decrease in the R-R interval is due to the rapid decline in arterial pressure (the relatively fast arterial blood compartment controls vascular resistances) before the effect of halothane on the baroreceptor-heart rate gain and set values can take effect (loop controlled by halothane concentration in the slower brain compartment). Stroke volume, on the other hand, constantly decreases with time, primarily due to a decrease in the reciprocal of ventricular compliance. Cardiac output increases initially, but soon decreases below the awake level and continues decreasing with time. The change in blood flows for the 0 \rightarrow 2.0 per cent step change in inspired halothane concentration are illustrated in figure 6. Blood flows to poorly perfused organs, fat, and heart muscle decrease with time, with most of the reduction in these flows occurring within the first 15 min. Well-perfused organ and muscle blood flows also decrease with time, but do not show the rapid initial decline. Unlike the other blood flows, the cere-

bral gray matter flow increases initially and remains at a higher level.

In figures 7 and 8 are shown the responses of alveolar halothane concentration and arterial blood pressure to a 0 \rightarrow 5.0 per cent change in inspired halothane concentration when the amplitudes of reciprocal compliances for the ventricles are controlled by the halothane concentrations in arterial blood, in cerebral gray matter, or in heart muscle, or by a combination of concentrations in these three compartments in equal portions. As the circulation becomes markedly depressed, the alveolar concentration suddenly increases (fig. 7), hastening the depression of the cardiovascular system. The decay time of arterial blood pressure (fig. 8) when myocardial compliance is affected by the concentration in arterial blood is considerably shorter than that when myocardial compliance is affected by the myocardial concentration of halothane. The decay time of arterial blood pressure during control by the concentration in brain is similar to that during control by the combination of compartments, although the initial reduction in arterial blood pressure is greater with the latter.

Discussion

The uniqueness of the present model lies in several areas: the use of a multiple model; the amalgamation of separate respiratory, circulatory, and uptake and distribution models; the demonstration of the complex interactions among the models and the large number of variables available; the pulsatile character of both the pulmonary and the circulatory models; the modulation of myocardial "contractility" and regional

vascular resistances by halothane concentration; the ability to select and weigh the compartments whose halothane concentrations modulate these variables; and the inclusion of a baroreceptor-heart rate loop whose slope and set point are influenced by the concentration of halothane.

The demonstration of the interaction between the cardiovascular system and the uptake and distribution of halothane is made possible by the use of a multiple model. Several excellent nonlinear models of uptake and distribution have been developed.^{19,21,22} Our models,^{11,12} however, are the only ones that use the multiple-model concept. In addition to its ability to delineate the interaction among disparate systems, there are other features and advantages of a multiple model. These have been previously described in detail¹¹ and are only outlined here: 1) Additional models can be relatively easily incorporated into a multiple model to make it more realistic or to take into account

new conditions. For example, we have added a carbon dioxide mass-transport model to the one described in this paper, with a resulting increase in appropriateness and versatility.²³ 2) New information, previously not available with single, linear models, can be obtained. 3) As a corollary of 2, a wider variety of experiments can be performed to test the different outputs of the model. In the case of the present model, these experiments can examine not only compartmental concentrations, but also the dynamic responses of the cardiovascular system to rapidly changing halothane concentrations.

Many of the features listed above contribute to the realism of the model. For example, the pulsatility in the cardiovascular and respiratory systems is represented. Pulsatile representations are more physiologic, and they are useful in demonstrating major cardiovascular and ventilatory responses to students and physicians. The output of the model resembles

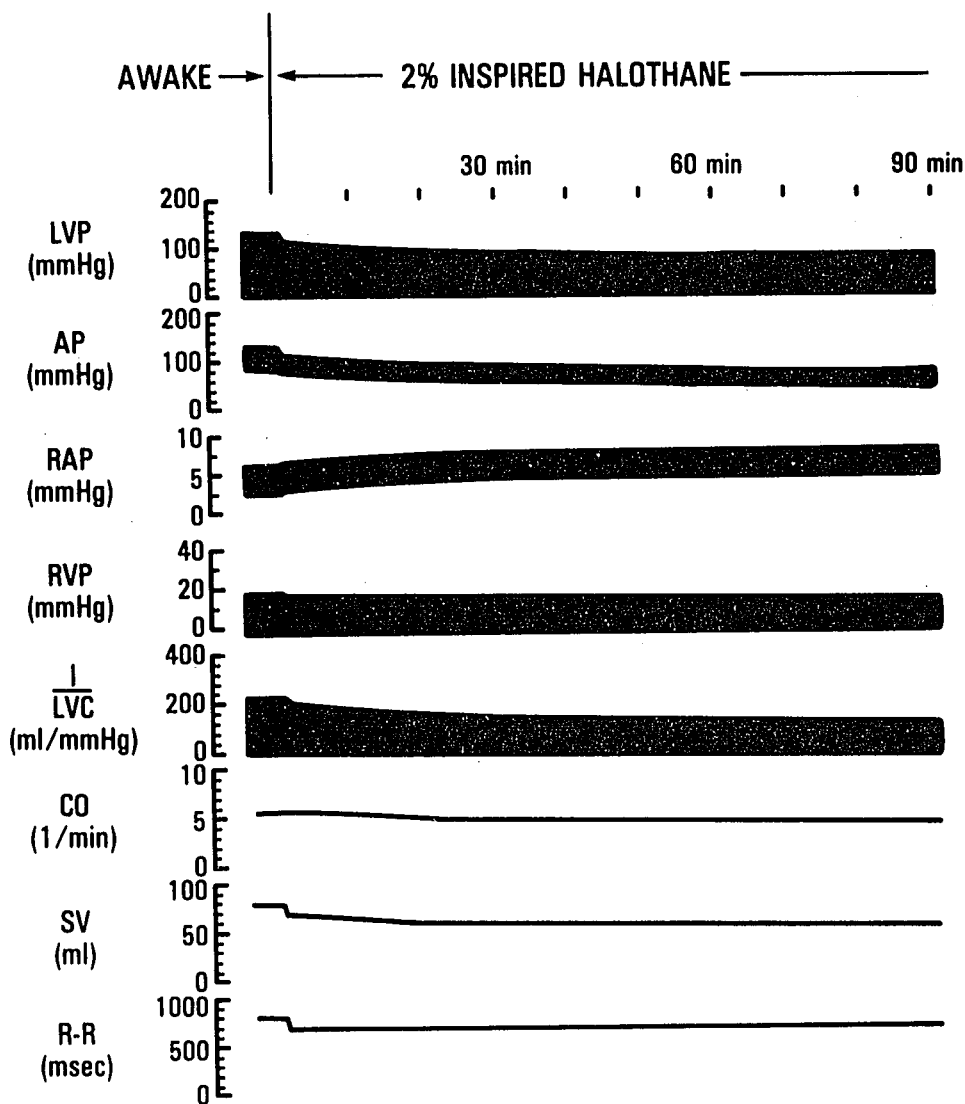


FIG. 5. Cardiovascular responses to a step change of 0 → 2 per cent in inspired halothane concentration. See figure 2 for abbreviations. Myocardial compliance is controlled by the halothane concentration in the cerebral gray matter. Notice that most of the responses occur early. Cardiac output (CO) changes very little.

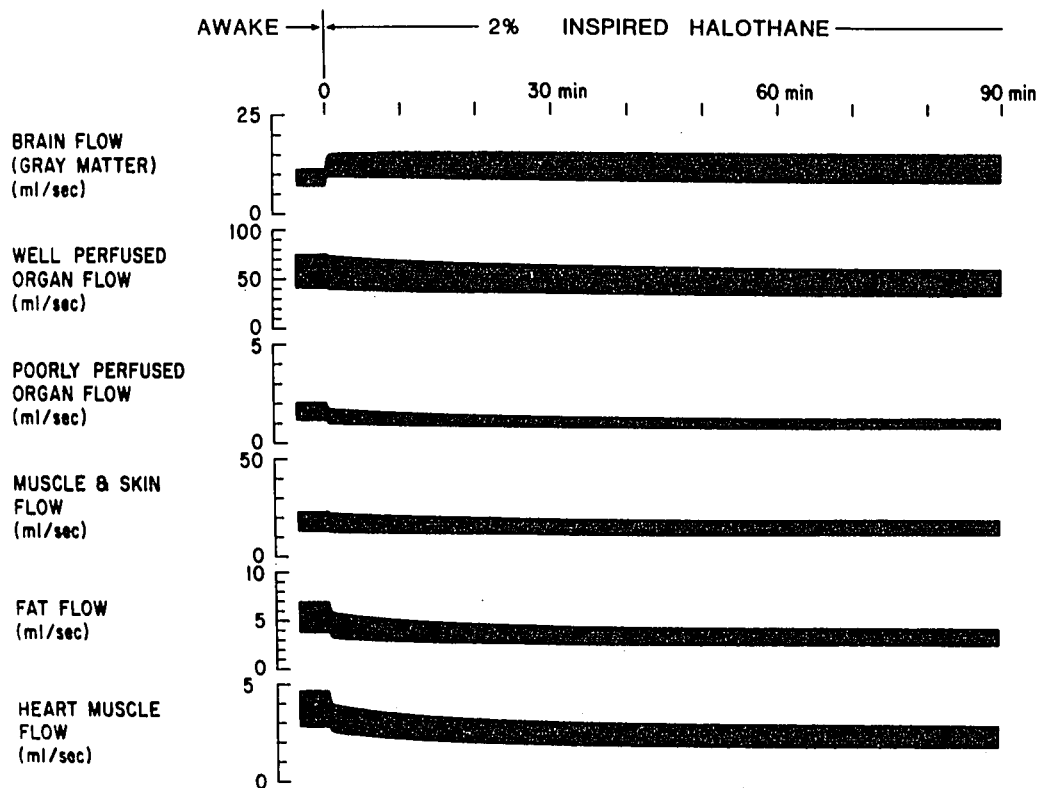


FIG. 6. Responses of regional blood flows to a 0 \rightarrow 2 per cent step change in inspired halothane concentration. Myocardial compliance is controlled by the halothane concentration in the brain gray matter. Notice that brain blood flow increases rapidly and remains elevated for the 90-min period.

the output of our monitoring systems. Thus, the utility of the model as a teaching device is greatly enhanced. The pulsatile events during cardiac and respiratory cycles admittedly have little or no effect on halothane uptake and distribution, however. An exception is the slight respiratory variation seen in alveolar concentration (figs. 4 and 7).

Although the present model has overcome many of the objections to previous models, it has presented new ones. The pulsatility in particular has created problems. An advantage of an analog computer is its extremely rapid rate of computation. Yet, in recording the cardiovascular phenomena onto a strip-chart recorder, we were limited by the frequency re-

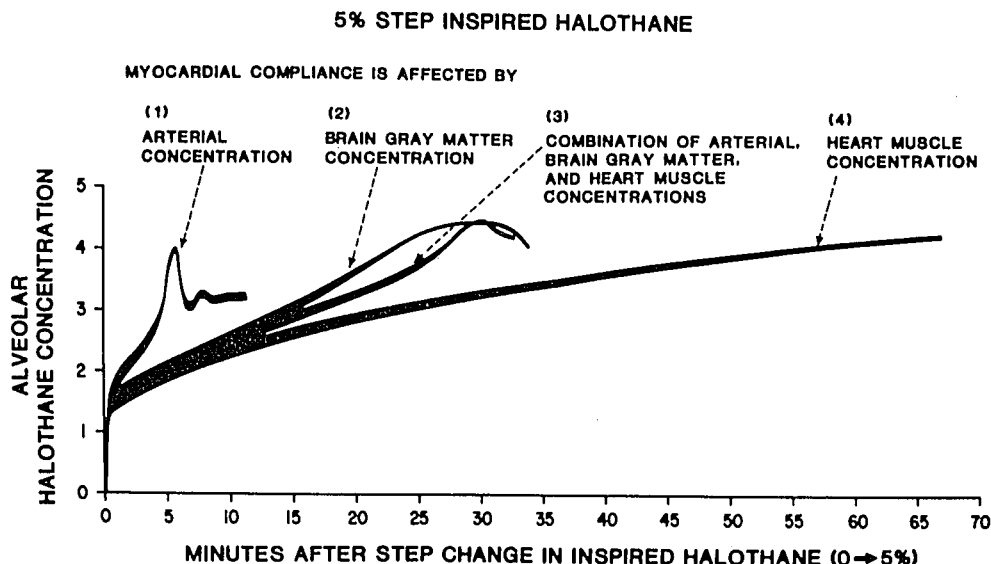


FIG. 7. Response of alveolar halothane concentration to a step change of 0 \rightarrow 5 per cent in inspired halothane concentration. As indicated by figures 2 and 3, 5 per cent halothane exceeds the lethal concentration. The arrows indicate the compartments that control myocardial compliance. The end of the line indicates the end of the animal. The thick line represents respiratory variations in alveolar concentration.

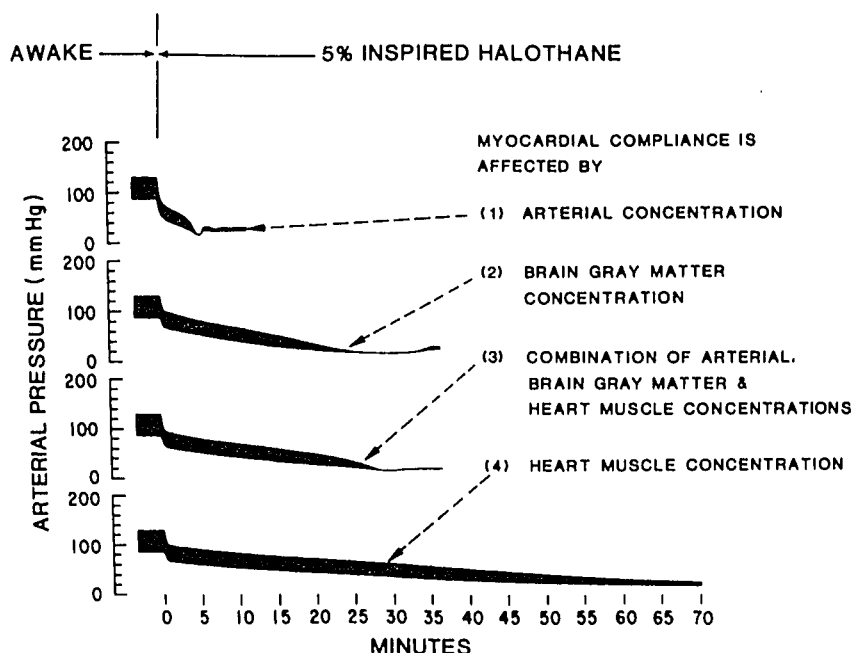


FIG. 8. Response of arterial pressure to a 0 \rightarrow 5 per cent step change in inspired halothane concentration. Myocardial compliance is controlled by the same series of compartments as in figure 7.

sponse of the pens. Thus, we were constrained to ten times real time, although faster times, such as 60 or 600, would have been more convenient. In addition, a large computer is necessary, decreasing the number of these devices available to implement the model. The hybrid computer we used, one of the largest in an academic institution in the United States, was pushed to its limit by this model. Thus, although pulsatility is elegant for teaching, it is probably not necessary for accuracy.

Portions of the model have been verified by several studies, both in our laboratories and in others. These include studies during steady-state,¹⁵ as well as step^{24,25} or sine-wave,[¶] administration of halothane. The step and sine-wave studies in particular are unique in that only with these models are the studies pertinent and the results capable of being evaluated. It must be recalled that the only cardiovascular effects of halothane directly programmed into the model were the modulations by halothane of "contractility," regional vascular resistances, and the baroreceptor-heart rate response—and these during periods of equilibrium only. Everything else was determined by the interaction among the models and their individual

parts. This is particularly important during rapid changes of anesthetic concentration.

For example, except for cardiac output, most of the cardiovascular changes demonstrated by our model occur early and rapidly following a step increase in halothane concentration (figs. 5 and 6). This is particularly true of cerebral blood flow (CBF), which shows an almost explosive increase (fig. 6). Albrecht *et al.*²⁵ also observed an abrupt increase in CBF when 2 per cent halothane was administered to conscious goats. In both model and goats, substantial increases occurred by 1 min, and the CBF essentially plateaued by 2 min. The increase in CBF in goats occurred while the animals were still conscious and standing. This phenomenon was predicted by our model, since at 2 min, the cerebral gray matter concentration was about 0.2 per cent (fig. 4), a concentration that is less than the "awake MAC" of 0.41 per cent determined in a study of human subjects by Stoelting *et al.*²⁶

To explain the early, abrupt increase in CBF does not require a special time-related vasodilating property of halothane, only that observed in the steady state by Wollman *et al.*²⁷ The phenomenon could be accounted for by a fast compartment to modulate vascular resistances and a relatively slow one to modulate "contractility" (equivalent to stroke volume in our model) and the baroreceptor reflex. We modulated changes in vascular resistances by the halothane concentration in arterial (arteriolar) blood, a "fast" compartment; stroke volume and the baroreceptor reflex by that in cerebral gray matter, a "slow" compartment. Thus, a decrease in cerebral vascular resistance

¶ Smith NT, Calverley RK, Coles JR, et al: The cardiovascular response to changing halothane concentrations in man, Abstracts of Scientific Papers. Annual meeting of the American Society of Anesthesiologists, 1976, pp 359-360.

** Smith NT, Fukui Y, Calverley RK, et al: The computer as a patient. Hemodynamic similarities between model and man, Abstracts of Scientific Papers. Annual meeting of the American Society of Anesthesiologists, 1978, pp 27-28.

would occur before any change in total flow (cardiac output, see fig. 5), and would explain why the majority of the increase in CBF occurs before the brain is anesthetized.

The major difference between Albrecht's results and ours was the relative steady-state increase in CBF, Albrecht observing a doubling of CBF, and our model predicting an increase of about 40 per cent. The discrepancy is simply related to the fact that we indirectly programmed steady-state values that were obtained from human studies²⁵ and that are considerably lower than the values Albrecht *et al.* observed in goats. Whether this difference is due to variations in species, techniques of measurement, or protocols is difficult to say. If we were to substitute the steady-state values from Albrecht's studies into our model, we should be able to imitate his results quantitatively as well as qualitatively.

The main difference between the protocol of Albrecht *et al.* and ours was that they allowed spontaneous ventilation, while we used controlled ventilation. The differences between the two modes of ventilation are discussed in a companion paper.²³

We are able, in this model, to assign the modulation of myocardial "contractility" and regional vascular resistances to any one or combination of three compartments: myocardium, arterial blood, and cerebral gray matter. To simplify matters, we assigned the modulation of vascular resistances to the concentration in arterial blood, assuming this concentration to reflect that in arteriolar muscle; in other words, we assumed that halothane exerts its control only by a direct effect on the arterioles. "Contractility" was modulated by the concentration of halothane in each of the three compartments separately (three runs), or equally proportioned in the three compartments (one run). We had hoped that our assigning the modulation of "contractility" and regional vascular resistances would help to provide insight into the mediation of the cardiovascular effects of halothane, namely, how much is due to indirect effects via the brain and how much to direct effects via the heart and vascular resistances. Modulation by a fast compartment (arterial blood) definitely produces results different from those produced by modulation by a slower compartment (myocardium) (figs. 7 and 8). It became apparent, however, that there was no unique solution; that is, an infinite number of combinations of compartmental control could produce the same result, at least so far as experimental precision was concerned. This conclusion is suggested strongly by figures 7 and 8, where the results obtained when

modulation of "contractility" was equally partitioned among the three compartments are shown to be similar to those obtained when modulation was confined to the brain. We can say, however, that modulation of "contractility" by halothane very probably does not reside exclusively in the myocardium or the arterioles, since the corresponding outputs shown in figures 7 and 8, as well as other outputs, such as sine-wave (Smith NT, Fukui Y, Coles JA: Unpublished observations), do not match those obtained in man.** The problem does become more intriguing in light of a recent article. Arndt and Freye²⁸ have been able to reverse the cardiovascular depressant effects of halothane in dogs by perfusing the fourth cerebral ventricle with (–)naloxone. Their studies suggest, as does our model, that the brain may play a significant role in the production of the cardiovascular effects of halothane.

The use of different compartments to modulate contractility and vascular resistance has led to some interesting results. For example, arterial blood pressure was partially controlled by a rapid compartment (vascular resistances modulated by halothane concentration in arterial blood). The baroreceptor reflex and stroke volume, on the other hand, were controlled by a slower compartment, halothane concentration in cerebral gray matter. Thus, as shown in figure 5, the increase in heart rate resulting from the decrease in arterial blood pressure was able to compensate for the decrease in stroke volume, so that there was little early change in cardiac output. This agrees with results of studies during step changes in halothane concentration, including induction, in normal volunteer subjects.^{24,¶}

Like previous models, our present model is a non-rebreathing system, primarily because we were more interested in refining the respiratory and cardiovascular aspects of the model, and it is easier to evaluate these experimentally without introducing the further complexities of a closed or semiclosed anesthesia system. Again, however, the multiple-model approach simplifies the incorporation of anesthesia systems and ventilators.

The possible impacts of many of the assumptions listed in the Methods section have been discussed previously.^{9,11,12,22} More recently, another problem has been raised by Allott *et al.*,²² who have presented compelling evidence that there is significant diffusion of halothane from muscle and kidney into fat. They could simulate this diffusion by diverting blood flow from the renal to the fat compartment and by increasing the Ostwald coefficient of the muscle compart-

ment. Although these maneuvers caused significant changes in uptakes into these compartments, they produced considerably smaller alterations in other compartments, such as arterial blood and brain. We have determined that large changes in blood flows to well-perfused organs produce relatively minor changes in uptakes into the arterial blood, brain, and myocardial compartments.^{11,††} The error introduced by the omission of the diffusion of halothane into fat is negligible for the brain²² and presumably so for the heart muscle compartment. Certainly, short-term discrepancies are minor. Since these compartments assume a major role in circulatory modulation, the inaccuracy produced in our model is probably slight, particularly when compared with deviations among individuals. Allott *et al.*²² suggest that cardiac output and alveolar ventilation have a considerably greater influence. Be that as it may, we plan to incorporate diffusion, as well as circulatory adaptation and metabolism, into our next model. The multiple-modeling concept renders these easier to incorporate than does a conventional model. The assumption that there is no impact of changes in CO₂ on the uptake and distribution of halothane is assessed by the model described in the companion paper.²³

In summary, we have described a hybrid computer multiple model of the uptake and distribution of halothane. The submodels are a circulatory model, a respiratory model, and a mass-transport model of halothane. The multiple model demonstrated very well the complex interrelationships among cardiac output, regional blood flow distribution, and the uptake and distribution of halothane. We examined the circulatory patterns produced by a step change in inspired halothane concentrations from 0 to 2 per cent. The initial, the late, and even the directional responses differed among the several circulatory variables. Changing the compartment (arterial blood, cerebral gray matter, or myocardium) whose halothane concentration affected myocardial compliance produced quantitative and qualitative differences among alveolar uptake and arterial pressure responses. The unique features of the model are the ability to add new models to the existing one, the modulation of "contractility" and regional vascular resistances by halothane concentration in any one or combination

of three compartments, and the pulsatile nature of the respiratory and cardiovascular recording.

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