DYNAMICS OF CHANGES IN CARBON DIOXIDE STORES

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The variations in carbon dioxide content of the body have been repeatedly investigated. There are good reasons for this continued interest since this information has become necessary to the physiologist who must decide the CO₂ tolerance of man exposed to confined spaces in submarines or space vehicles. To what extent does man act as a CO₂ absorber? At what rate can he store his chief waste product, CO₂? At what rate can he lose the stores which he normally carries with him? What are the physiological limits of CO₂ store loss and CO₂ store gain? These are but a few of the questions yet to be answered.

While there are many approaches and problems which can be reviewed, our main objective is to discuss the factors which determine the speed of CO₂ store accumulation or depletion. A vast amount of data on this topic has accumulated, but the number of articles is less impressive than the divergent results.

In one of the first reports, Adolph and associates commented on their own findings by saying that they "did not feel confident that in 33 minutes saturation was completed." Many of the articles published since deal with procedures lasting only a few minutes, while others required several weeks. The results indicate that the CO₂ storage capacity of the whole body mass may vary from 0.3 to 11.6 ml. of CO₂ which can be stored per kilogram of body tissue for 1 mm. change in PCO₂ (ml./kg. body weight 'mm. CO₂').

One attempt to describe the behavior of CO₂ store changes was presented earlier. This model treated all the tissues as a single compartment, described the experimental data obtained in anesthetized dogs, and yielded results essentially similar to those obtained by others in cats. More recently one of us suggested that the discrepancies of CO₂ storage noted above must be associated with the equilibration period and that the dynamics of CO₂ store changes must consider the body as composed of various compartments each with its own CO₂ storage capacity and perfusion rate. Recent careful experiments also indicate that CO₂ store changes in man do not fit the single compartment concept.

This review will describe a model, crude as it is, which may provide a reasonable description of the CO₂ storage process and will compare its behavior with experimental results in the literature. Any model system has its limitations; to recognize its weaknesses is paramount. Yet we believe that our model provides an explanation for the variance in experimental results. Above all, it has pointed out that equilibration following a change in CO₂ environment requires hours for completion, a period far beyond most of the previous studies.

Our model is an electronic analogue superior to our previous mechanical models because its behavior can be presented for solution to a computer.

After comparing results of the analogue with existing physiological data, we have concluded that the analogue is a good representation of the problem, and we are justified in explaining the existing physiological data on the basis of our computer results. In view of the simplifying assumptions made, the quantitative results may be challenged, but we hope to point out the most critical physiological parameters in CO₂ retention or CO₂ loss.

A MODEL FOR CHANGES IN CARBON DIOXIDE STORES

Let us first consider the simplest model which will demonstrate changes in CO₂ stores. Here the whole body is considered as a common pool, where CO₂ is in physical solution and in chemical combination. The total amount is a function of CO₂ tension of the alveolar gas or of the arterial blood. Under steady state conditions the amount of CO₂ produced by the body is equal to that expired, indicating that CO₂ stores remain unaltered. When alveolar ventilation is changed, a new alveolar tension is reached and the body stores

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readjust at a different level, the new steady state. This re-equilibration of body stores will require an elevation in CO₂ content if the alveolar CO₂ tension has increased (hyperventilation). Since the additional CO₂ stored is part of the metabolic production, the expired CO₂ must be reduced by an equal amount. Hyperventilation will cause opposite changes.

A mechanical model of this simplified description similar to the one previously described \(^2\) is given in figure 1. A large reservoir represents the CO₂ content of body tissues, the flow of liquid into this reservoir is the CO₂ production and the outflow through a resistance, the CO₂ output through alveolar ventilation. The height of the liquid in the reservoir is the CO₂ pressure and the reservoir content represents the CO₂ body stores. When the system is left undisturbed for a sufficient time the liquid level will stabilize at a height at which the hydrostatic pressure in the reservoir will force an amount equal to the inflow through the outlet tube. Under these conditions the level in the reservoir will not change and a steady state will obtain. Variations in alveolar ventilation will be represented by a change in resistance to the outflow. If this resistance is decreased by half its value (equivalent to doubling the alveolar ventilation), the level of liquid will decrease. This will finally stabilize at half its original height, indicating that only half the pressure is necessary to drive the same liquid flow through the decreased resistance. During the equilibration period (the unsteady state) the outflow will be larger than during either initial or terminal steady state, the increment representing the decrease in content of the reservoir.

![Fig. 1. A single compartment model for CO₂ stores of the body. The upper half represents the hydraulic model, and the lower half an electronic analogue. For details see text.](image)

![Fig. 2. The continuous line represents the CO₂ dissociation curve of blood. The dotted line is a straight line having a slope of 45 vol. per cent/mm. P₁₂. The error introduced by assuming this to be the constant slope of the blood curve between 30 and 80 mm. P₁₂ is small compared to the variations in other biological parameters used.](image)

The changes which occur in the height of the reservoir (Δh) correspond to changes in CO₂ pressure (ΔP₁₂), and changes in volume of the liquid (ΔV) are equivalent to changes in the CO₂ content of the stores (ΔC₁₂). Therefore, both ΔC₁₂, ΔP₁₂, and ΔV, Δh (which represents the cross-sectional area of the reservoir) describe the slope of the dissociation curve of the CO₂ stores of the body. Only as long as the slope is constant (linear dissociation curve) the cross-sectional area of the reservoir is fixed. While we know that the dissociation curves of blood and tissues are not linear throughout, there is a tendency for linearity over a range of 30 to 80 mm. P₁₂ (fig. 2). In all our subsequent considerations we have assumed linearity in order to simplify our procedures.

With such a model, following a sudden change in outflow resistance (change in alveolar ventilation) the changes in CO₂ stores will be a simple exponential of time. When these changes are shown on a semilogarithmic plot as a fraction of the final change, versus time, a straight line is obtained. This type of behavior has been described in detail previously.\(^2\)

An electrical analogue can also be designed and appears in figure 1 under the hydraulic model. This analogue is identical in its opera-
FIG. 3. An electronic analogue of CO₂ stores: the series model. In this the drop of CO₂ tension from tissues (assumed to be at mixed venous blood tension) to the alveoli is inversely related to the cardiac output. The drop in pressure between alveoli and atmosphere is inversely related to alveolar ventilation. Alveolar gas and arterial blood (right hand capacitance) are equilibrated at alveolar CO₂ tension, the rest of the body at mixed venous pressure tension.

Its advantage lies in the fact that it can be more easily modified in a subsequent step to represent more faithfully the biological system. The CO₂ production of the body is now represented by the output of an electrical source (current intensity), the body compartments by a capacitor of capacitance C, and the alveolar ventilation by a resistance, R. The CO₂ tension is the potential. The total charge on the capacitor is the CO₂ store, while the capacitance is now the slope of the dissociation curve. Again, charge and potential will be altered by changes in resistance and the response to a stepwise change will be exponential. The time course of the change is best expressed by the time constant, which is the time necessary to produce (e−1) e (approximately 63 per cent) of the total content change. As an example, if the total change is 4 liters, the time constant is the time required to obtain a change of .63 x 4 or 2.52 liters. In a linear system this time constant, T.C., is equal to R x C.

Although either the hydraulic or the electronic model allows a description of the problem, they are inadequate for accurate estimation of changes. The models have assumed that the partial pressure of CO₂ with which the whole body has equilibrated is the alveolar tension. This is manifestly incorrect since a CO₂ gradient from tissues to alveolar gas is necessary in order to eliminate CO₂. To reproduce this in the model a double compartment has been described, the assumption being made that the tension in mixed venous blood is a good estimate of the mean CO₂ tension of tissues. The bulk of the stores was assumed to be equilibrated at that particular tension, with only a minor fraction, representing arterial blood, equilibrated at PAO₂. The electrical analogue appears in figure 3.

Our model appears more complex than the one previously described only until the appropriate figures are considered. The pressure decline from tissue to alveoli is of the order of 6 mm., while the alveolar-atmospheric pressure difference is 40 mm., which is to say that the resistance added by introducing the circulation is small. Similarly, the fraction of stores equilibrated at alveolar pressure is only a minor one. The system should behave therefore very similarly to the single compartment system and under certain conditions has proved to discharge accordingly.

The Multiple Compartment Model. In the single compartment system the change in vol-

### Table 1

**Storage Capacity (Slope of the Dissociation Curve) of the Body**

<table>
<thead>
<tr>
<th>Author and Reference</th>
<th>Species</th>
<th>Duration of Experiment, minutes</th>
<th>Slope, ml. kg. min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Mithofer (1)</td>
<td>Man</td>
<td>1-5</td>
<td>.46</td>
</tr>
<tr>
<td>B. Klocke and Rahn (8)</td>
<td>Man</td>
<td>3-8</td>
<td>.80</td>
</tr>
<tr>
<td>C. Brockhurst and Henderson (9)</td>
<td>Man</td>
<td>2-3</td>
<td>.50</td>
</tr>
<tr>
<td>D. Schaefer and Alvis (10)</td>
<td>Man</td>
<td>33</td>
<td>2.10</td>
</tr>
<tr>
<td>E. Lillicraft and Balke (11)</td>
<td>Man</td>
<td>30</td>
<td>3.8</td>
</tr>
<tr>
<td>F. Vance and Fowler (5)</td>
<td>Man</td>
<td>20</td>
<td>1.30</td>
</tr>
<tr>
<td>G. Vance and Fowler (5)</td>
<td>Man</td>
<td>60</td>
<td>2.05</td>
</tr>
<tr>
<td>H. Farhi and Rahn (2)</td>
<td>Dog</td>
<td>30-45</td>
<td>1.50</td>
</tr>
<tr>
<td>I. Shaw (5)</td>
<td>Cat</td>
<td>30-90</td>
<td>1.60</td>
</tr>
<tr>
<td>J. Shaw and Mosser (12)</td>
<td>Cat</td>
<td>100</td>
<td>1.80</td>
</tr>
<tr>
<td>K. Freeman and Fenn (13)</td>
<td>Rat</td>
<td>several weeks</td>
<td>up to 11.6</td>
</tr>
</tbody>
</table>
### TABLE 2

**Carbon Dioxide Stores of the Body by Compartment**

| Electronic Equivalent | A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R |
|-----------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Blood Volume**      | 2490 | 2410 | 2140 | 1890 | 1521 | 1180 | 1000 | 840 | 700 | 600 | 500 | 400 | 300 | 250 | 200 | 150 | 100 | 50 |
| **Change**            | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| **Capacitance**       | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| **Resistance**        | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| **Time Constant**     | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |

* If bone is excluded, the "total body CO₂ store" (soft tissue) is 16.6 liters.

Columns (A), (C), and (D) were obtained from the Handbook of Biological Data. Columns (B), (E), and (M) were obtained from Rahn. Column (F) indicates the amount of blood equilibrated with a tissue or organ present in the venous circulation. It is assumed proportional to the perfusion of the organ and is calculated as 1.500 X (J). Column (G) is calculated as (B) / (C). Column (I) is derived by adding (F) to (J) or which is assumed to be the arterial blood CO₂ content. Column (H) is obtained by multiplying (B) by 0.0015 (which is assumed to be the slope of the blood dissociation curve), and adding the figure obtained to the arterial PCO₂ assumed to be 10. Column J is calculated as (E) X (G) X 1000. Column K is equal to (B) X (G) X 1000. Column L is the sum of (I) plus (K). Column N is derived by multiplying (M) X (A). Column O is 0.005 X (I). Column P is the sum of (N) plus (O). Column Q is 0.0015 X (G). Column R is (P) X (Q).

The electronic model (fig. 3) by breaking down the main capacitance, that of the tissues, into separate components, each one being connected to the alveoli independently of others. With this in mind the various organs of the body have been tabulated separately (table 2). In this each major organ or tissue has been recognized as an individual equilibrating system, provided all the physiological parameters necessary were available. These included weight, CO₂ production, blood flow, CO₂ content, and the dissociation curve of this organ. From these data additional figures can be calculated. The electrical analogues are as before:

- CO₂ production—current intensity
- PCO₂—potential
- CO₂ content—charge
- Slope of CO₂ dissociation curve—capacitance.
Since our computations, results and conclusions hinge on the values appearing in table 2, a critical discussion of these parameters appears in the appendix. We hope that in time more correct values may be obtained and substituted.

Two lines in the table are incomplete. The first one is hump. Although hump is the major CO₂ reservoir there is no agreement on whether or not the CO₂ content is related to P_{\text{H}}^{12}. It is accepted, however, that these changes are limited, if they exist at all, in experiments lasting only a few hours. Body fat CO₂ changes have also been excluded from our final calculations. The amount of CO₂ dissolved in fat is far from negligible since \( \alpha \) for animal fat is about 0.9 (nearly twice as high as for CO₂ in water). However, fat is poorly perfused and cannot contribute much to changes in stores unless considerable time is available. If perfusion to body fat could be assessed, the adipose tissue could have been included in the computations. Thus, whereas the "total" CO₂ content (bottom of column) indicates the total CO₂ content for the whole body, "total" changes (sum of figures in column) are calculated to the exclusion of bone and fat, which are assumed to be so slow as to be negligible.

Resistance to CO₂ transport, the accepted ratio of pressure differential to flow, is calculated by using the difference between venous and arterial P_{\text{CO₂}} as \( \Delta P \), and the amount of CO₂ transported per unit time (which is the CO₂ production of the organ) as \( \Delta T \). This is also equal to the inverse of the product of organ flow times the slope of the CO₂ dissociation curve.

The product of the resistance and capacitance determines the time constant. It is this parameter which determines in the last analysis how effectively a compartment can use its storage capacity. This is obvious when we consider that regardless of the dissociation curve of an organ, the CO₂ discharged from the stores (as would occur in hyperventilation) must be discharged through the circulation. A low perfusion (indicated by a high resistance) may become the limiting factor in stores displacement. Conversely, when perfusion is high, the total capacitance of an organ can be brought into play rapidly. Muscle is the largest of all the capacitances involved (table 2).

Because of this its time constant is extremely high, compared to other organs. Thus, electronically it became apparent that the properties of the system must be affected to a great extent by variations in the muscle system. Whenever resistance of the muscle compartment is decreased, a similar decrease in time constant will occur and the presence of muscle capacitance will be more effective.

The physiological reasoning is as follows: the muscle mass, representing 40 per cent of the body weight, is the largest buffering pool of all organs considered. It is therefore obvious that whenever the alveolar CO₂ tension will change, most of the changes in total body CO₂ (charge) content will be due to changes in muscle CO₂. However, it is also evident that unless blood flow to muscle is proportionate to its storage capacity, perfusion becomes the limiting factor. When this perfusion is low, changes in muscle CO₂ will be slow. If perfusion is increased, CO₂ can be moved more easily from or into the muscle. Blood flow to muscle was therefore one of the parameters we chose to alter, thus changing the time constant. An analogue designed according to values in table 2 was assembled with some modifications. The electronic characteristics of the computer used have been described by Spangler and Snell. On this analogue we conducted three series of determinations, one with a muscle blood flow of 850 ml. minute, which is the basal flow of a second one in which this was reduced to 25 per cent of this value, which might indicate what would be expected if blood flow to muscle decreased (shock, anesthesia); and a third one with a blood flow of muscle of 2500 ml. minute, which would be comparable to the result of moderate muscle activity.

In each series the following experiments were presented to the computer and compared with data from the literature: (a) hyperventilation, doubling the alveolar ventilation; (b) hyperventilation, decreasing alveolar ventilation to 50 per cent of initial value; (c) breath holding; (d) rebreathing in a 10-liter bag; (e) rebreathing in a 20-liter bag; (f) rebreathing in a 40-liter bag; (g) rebreathing in an 80-liter bag.

In each case the time changes in potential in the separate compartments were recorded.
DYNAMICS OF CHANGES IN CO₂ STORES

Fig. 4. Electronic model of CO₂ stores—multiple compartment analogue. This differs from the preceding model by the fact that the bulk of the body has been divided into separate compartments, all discharging in parallel into the alveolar space. The figures appearing in each compartment refer to the parameter appearing at the same height on the left (physiological terms) or at the right (electronic equivalent).

By multiplying the change in potential (partial pressure) by the slope of the "total CO₂ dissociation curve" of the compartment (capacitance), the changes in CO₂ content of the compartment (charge) could be calculated. Adding the changes in all the compartments at any given time gives the change in body CO₂ content at that instant.

RESULTS

Effects of Changes in Muscle Perfusion. Figure 5 shows the results of a fixed degree of hypoventilation under two of the conditions studied (a—basal perfusion to muscle; b—muscle perfusion decrease). In either case the alveolar ventilation has suddenly been reduced to one-half its normal value, the CO₂ production remaining constant. This will eventually double P_{A\text{CO}_2}. In each half of the figure there are two curves. The continuous line represents the changes in P_{A\text{CO}_2} going from 40 to 80, while the dashed line represents the changes in stores.

The initial and final points are the same in the two halves of the figure. However, the time course of the events varies greatly. Under basal conditions there is a rise in P_{CO_2}, with slower changes in content. The right half of the figure shows gross deviations. The change in alveolar CO₂ is abrupt at first, and tails off with a slowly ascending plateau. This shape is typical of any record obtained when discharging a system in which two components with dissimilar time constants are set in paral-

Fig. 5. Hypoventilation experiment. The left figure a describes the time course with basal blood flow to muscle. The right figure b, drawn at the same scale, shows the effects of reduced perfusion to muscle. In each figure the continuous line represents the P_{A\text{CO}_2} changes, and the dashed line, the stores CO₂ increase. For details see text.
Fig. 6. Changes in slope of the body CO₂ dissociation curve with time. The middle line is the expected change with basal muscle perfusion, the one above it the expected change with increased muscle perfusion, and the lower one the changes with decreased muscle perfusion. Letters designate the experimental data from table 1.

The first part represents essentially the fast component, while the second reflects the slow compartment. Relatively few readers may be familiar with "CO₂ washout curves" or "CO₂ wash-in curves" (as the ones presented). However, nitrogen washout curves are more customarily seen. They represent essentially the same situation. When all alveoli are similar in their properties a uniform washout curve is to be expected. When there are gross differences between various elements, the multi-compartment curve with its initial rapid drop and subsequent plateau is encountered. This is what occurs to PₐCO₂ when the time constant of the muscle mass is grossly disproportionate to that of the other elements. In this case the CO₂ content of the body (CO₂ retained by stores) rises at a slower rate than before. The discrepancy in time changes between the two parameters becomes evident.

The data reported in the literature are usually expressed in its final form as changes in CO₂ stores/kg. body weight/mm. PₐCO₂. This information can be calculated from the curves appearing in figure 5. At any given time the change in stores CO₂ can be measured, divided by 70, to give the change per kilogram, and then divided again by the concomitant change in PₐCO₂. A curve showing the change in calculated values versus time can be constructed from each of figures 5a, and 5b, as well as from hypoventilation with increased muscle perfusion. These curves are shown in figure 6, in which the "storage capacity" is plotted versus time. This figure shows that if our model is an adequate reflection of the experimental conditions, the storage capacity of the body should indeed vary with time. These variations are due to the lag in store changes versus alveolar CO₂ tension changes. A large resistance to blood flow in the muscle (decreased flow and large time constant) will increase this lag and therefore the time needed to obtain true equilibrium.

The letters appearing in figure 6 represent some of the data from table 1 and show that the discrepancies between experimental results can be explained by differences in equilibrating period and in muscle blood flow. It is interesting to note that points H, I and J pertain to animals anesthetized with barbiturates and are in agreement with a decreased blood flow to the muscle. On the other hand, the data on unanesthetized humans are compatible with a muscle blood flow equal to or higher than basal value.

Figure 6 has an even greater significance when analyzed in conjunction with figure 5. Alveolar ventilation is a calculated value; in physiological experiments there is no method which will produce an exactly predetermined change in alveolar ventilation; therefore the final PₐCO₂ cannot be predicted. Thus the decision to assume that a new steady state has been achieved must be reached solely on the basis of the fact that the alveolar CO₂ tension remains steady. Figure 5 will show that at low blood flow to the muscle the CO₂ tension will tend to plateau early. This is obvious when we bear in mind that this is the condition in which CO₂ coming from muscle is just "trickling" to the alveoli and does not affect measurably the PₐCO₂. As an example, if in an experiment the new steady state was defined a priori as the condition at which PₐCO₂ varies by 1 mm. or less over a 15-minute period, experiment 5a would have been terminated at 135 minutes, while experiment 5b would have been stopped at 60 minutes, the respective storage capacities being 2.2 and 1.6 mL/kg./1 mm. PₐCO₂.

Effect of Alveolar Ventilation. In the overall analysis CO₂ has to be carried from muscle


into as well as out of the alveoli. Thus alveolar ventilation will be a factor in determining the speed of equilibration of muscle CO₂ stores. In the analogue this is equivalent to describing the discharge of the muscle capacitance through two resistances in series. Thus the curves appearing in figure 5 pertain specifically to an alveolar ventilation of 50 liters. The effects of differences in alveolar ventilation have been computed but are too intricate for this review. The basic information is that the importance of alveolar ventilation varies inversely to muscle circulation, which is to say that when the limiting factor to CO₂ movement is mainly in muscle circulation, the total outflow resistance cannot be affected greatly by alveolar ventilation, which plays a small role.

Correlation with Existing Data. Before trying to apply to the living animal the conclusions derived from the analogue, it is necessary to show that when the latter is programmed to duplicate experimental conditions, the computer results are compatible with the physiological data.

The basic assumption made was that each segment of the body reacts to changes in CO₂ tension by varying its CO₂ content in the way an R-C system behaves. Bortolin and others have introduced C14O₂ in the rectum of a dog between two ligatures and watched the elimination of labeled carbon dioxide through the lungs. When their data were plotted on a semilogarithmic scale, a rapid linear decrease is evident for the first 80 minutes. The slower phase appearing at that time is probably due to elimination from other body compartments which had retained C14O₂ which had passed through the lungs. A similar record is obtained from the analogue when an additional charge is added to one of the capacitances.

Nichols has studied equilibration of some of the body CO₂ stores in rats. The data for muscle CO₂ is essentially similar to that obtained on the computer and indicate that in the unanesthetized rat several hours are required for equilibration.

Vance and Fowler studied serially changes in stores and in P CO₂ following a stepwise change in alveolar ventilation. Figure 7 shows their data on CO₂ stores changes versus time, with the appropriate curves from the computer added.

Mitchofer has conducted experiments on rebreathing oxygen from bags containing various volumes of oxygen. The alveolar ventilation was increased about tenfold at the beginning of the experiment and maintained throughout the rebreathing period. Figure 8 shows the time changes in PA O₂ in Mitchofer’s experiments and those obtained from the computer data under simulated decrease in muscle perfusion.
It would appear therefore that the analogue is a fair reproduction of the physiological experiments and that the conclusions from the computer data can be applied to animal experiments, within the limiting frame of our assumptions.

A good example of the limiting value of our assumptions may be found in the excellent work of Lillehei and Balke which disagrees with our calculated curves. The discrepancy is large (3.8 ml. kg. mm. P<sub>1</sub>) and not unexpected since in the experiment the final P<sub>1</sub> was about 25 mm. where the slope of the dissociation curve is higher than .45 vol. per cent. mm. The difference between actual and calculated results can be explained on this basis.

**Effects of Direction of Change.** When ventilation is decreased, additional CO<sub>2</sub> must be retained by the stores. This CO<sub>2</sub> must either be produced locally or brought in by blood. If perfusion is low, metabolism will be the only possible source of CO<sub>2</sub> and may become a limiting factor in the speed of stores readjustment. Obviously, the same problem does not arise during an increase in ventilation when there is loss of previously stored CO<sub>2</sub>.

**Conclusions**

The analogue computer has allowed us to single out a certain number of parameters which must influence CO<sub>2</sub> stores equilibrium. The crucial point appears to be the effect of muscle perfusion on the "functional" storage capacity of the body. It is this perfusion which changes potential storage capacity into an actual buffering system. If this perfusion differs between two experiments or changes during an experiment, an entirely new set of conditions will prevail and the results must be viewed accordingly.

Even under the most favorable conditions the body CO<sub>2</sub> stores must require several hours to adjust. With few exceptions all the data in the literature must be accepted as representing incomplete experiments in which time limitations did not allow full equilibration of the body stores.

There are large cyclic variations in alveolar CO<sub>2</sub> tension. In the light of our previous discussion we would postulate that since it takes the CO<sub>2</sub> stores several hours to readjust, there is a continuous change in stores, the steady state—if it ever occurs—being the exception rather than the rule.

The question which must be answered next is obvious: how long should re-equilibration be carried on? The dangers of relatively short experiments are clear. However, prolonged experiments suffer from drawbacks which are not less serious. Except in sacrifice experiments, where the whole animal or parts are actually analyzed for CO<sub>2</sub> contents, the stores changes are calculated as the difference between actual CO<sub>2</sub> output and metabolic CO<sub>2</sub> output. The assumption of a basal CO<sub>2</sub> output over a period of several hours may be dangerous.

An entirely different objection for long equilibration is the fact that any change in CO<sub>2</sub> will alter the acid-base balance of the body and bring into play compensatory mechanisms. Nichols' data show that after 5 hours of exposure to high CO<sub>2</sub> the muscle CO<sub>2</sub> has readjusted and remains practically unchanged. There is a questionable change in brain CO<sub>2</sub> but a significant, steady increase in blood CO<sub>2</sub>. This must represent cation retention, as is usually found in respiratory acidosis. Extrapolation of the blood CO<sub>2</sub> content curve between 5 hours and 50 hours to time 0 reveals values measurably lower than at 5 hours, indicating that even during this time readjustment is already taking place.

Thus the investigation of the body CO<sub>2</sub> stores presents a real dilemma. Whether it is better to run the risk of terminating the experiment too soon, before complete equilibration, or chance the alternate danger of modifying the biological system will depend greatly on the investigator and the specific problem at hand.

**Summary**

The wide scatter in reported CO<sub>2</sub> storage capacity of the body must reside in a factor or factors which have not sufficiently been taken into account. In order to determine what these factors may be, data for the CO<sub>2</sub> storage capacity of various organs and their perfusion were collected. Using these data an electronic analogue was constructed. By simulating various procedures and varying the parameters, several experimental conditions were reproduced. Since most of the CO<sub>2</sub>
storage capacity resides in the muscle, per-
mission of the muscle mass will determine the
rate at which this storage capacity may be
brought into play. At rest, re-equilibration is
always a lengthy process, requiring several
hours. Under these conditions it should be
concluded that most of the data in the litera-
ture were obtained from experiments where not
enough time had been allowed for equilibration.

APPENDIX

Construction of table 2 and of the analogue
were limited by the lack of specific information
concerning certain organs or tissues of the body.
Several assumptions were required and some
simplifications have been made. Under these
conditions it becomes evident that the table
represents more a method of thinking than a
compilation of finalized data.

The first column in the table indicates the
parameter studied and the unit in which this
parameter is given. In the legend either the
source or the method of obtaining the parameter
is given. Basic information was taken from two
sources, and all other values were calculated
from these according to the formula shown.
When any data were used in the analogue the
equivalents appear under the parameter. All the
other rows represent compartments, i.e., tissues
or organs.

Exclusion of bone and fat from the table dis-
trust considerably calculations of total body CO₂
content. However, it is probable that only a
minimal error is introduced in the calculation of
changes in CO₂ content (see text).

The simplification inherent to a classification
of the whole body (except bone and fat) in five
compartment is probably more damaging. Every
compartment is assumed to be uniform, which is
probably erroneous. In order to be able to
isolate elements the basic data for each must be
available. The error resulting from "idealizing"
compartment by assuming uniformity cannot be
predicted.

The first four parameters considered present no
problem. Since the body is dealt with as separate
compartment, the blood returning from each is
considered separately. This "equilibrated blood
volume" appears in line V. Its calculation is
based on the assumption that each compartment
contributes to the venous blood volume in propor-
tion to its perfusion. The venous blood is as-
sumed to be 75 per cent of the total volume, or
3,500 ml.

Using the Fick principle, the CO₂ output of
every organ and its perfusion and the CO₂ content
in the venous blood can be calculated, assuming
an arterial content of 48 vol. per cent.

The partial pressure of CO₂ (line VII) is based
on the assumption of an arterial P_{CO₂} of 40, a
depth of the blood CO₂ dissociation curve of
.45 vol. per cent/mm. P_{CO₂}, and on the venous
CO₂ content calculated above. The partial pres-
sure of CO₂ in the tissue is not known. Recent
studies have shown that lymph has a P_{CO₂} higher
than that of the venous blood draining the same
area. If lymph gives a good indication of tissue
tension, a large error in organ CO₂ content is
probably introduced when one assumes tissue
tension to be that of venous blood. However, if
the difference in CO₂ tension between a com-
partment and the blood draining it remains con-
stant (which is the assumption made), then
changes in tissue CO₂ content can be calculated
using venous P_{CO₂} values. The slope of the dis-
sociation curve of the various tissues does not
introduce any additional assumption. However,
as better analytical methods become available,
some of the figures will have to be revised.

If CO₂ is stored in the tissues as bicarbonate,
this will necessitate hydration and the lack of
bicarbonate anhydrase in a given tissue may prove
a limiting factor in the storage capacity of an
organ.

The slope of the dissociation curve of any
issue is assumed to be constant. This is not
necessarily correct and may be affected by one of
the following: (a) overall change in buffering
capacity, as occurs during compensation of respira-
tory acidosis, (b) transfer of electrolytes from
one compartment to another, (c) production of
metabolites (such as lactic acid) which can
displace CO₂ from bicarbonate, and (d) change
in compartment volume.

Calculations for the alveolar compartment are
sharply different. The equilibrated blood volume
is assumed to be the total arterialized blood
volume.

The kidneys have been excluded from the
"other" compartment since their perfusion is
extremely high (very low resistance) and their
capacitance is necessarily small. Thus their
time constant is practically nil. The capacitance
of this system (which is mostly in the equilibrated
blood volume) has therefore been added to that
of the alveolar compartment.

Since the time constants of the heart, brain
and "other" compartments are essentially similar,
it is possible to replace these three compartments
by an "equivalent compartment" without changes
in the results or conclusions.

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REFERENCES

1. Adolph, E. F., Nance, F. D., and Shilling,
M. S.: Carbon dioxide capacity of human
body and progressive effects of carbon di-
sioxide upon breathing, Amer. J. Physiol. 87:
532, 1929.


10. Schaefer, K. E., and Alvis, H. J.: Effect of inhalation of low oxygen concentration (10.5% O2 in N2) over a period of 33 minutes on respiration, pulse rate, arterial oxygen saturation and oxygen uptake, Naval Medical Research Laboratory Report No. 175, 10: 76, 1951.


