CARBON DIOXIDE AND RESPIRATION IN ACID–BASE HOMEOSTASIS

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RESPIRATORY stimulation and dilatation of brain vessels are among the most prominent effects of carbon dioxide administration but for neither is the ultimate mechanism of the CO_2 effect known. Administration of CO_2 results in two kinds of change. The first, elevation of the CO_2 partial pressure, can be considered a physical alteration; it increases the physically dissolved CO_2 which may possibly exert inert gas effects. However, physically dissolved CO_2 is not entirely inert. Through hydration of CO_2 molecules, the physical phenomenon of gas pressure is linked to chemical formation of hydrogen and bicarbonate ions. These ions offer a second, and possibly independent, means whereby CO_2 may alter physiological processes.

Data and questions pertaining to the relative importance of the physical and chemical influences of CO_2 in respiratory and brain circulatory control have been elsewhere reviewed[1, 2] and will not be elaborated here (see also p. 664 of this symposium). However, a recent quantitative study in man [3] emphasizes that in a variety of acid-base alterations (including bicarbonate administration during CO_2 inhalation [3], diabetic acidosis [4] and experimentally induced metabolic acidosis [5, 6]) it is necessary to consider only changes in hydrogen ion concentration to account quantitatively for respiratory changes observed in these conditions. Conversely, relaxation of brain vessels appears to be related quantitatively to change in CO_2 pressure and to be uninfluenced by small alterations in blood $[H^+]$ or $[HCO_3]$.[2, 3, 7]

Recognizing the great dependence of $[H^+]$ and $[HCO_3]$ upon the physical pressure of carbon dioxide (P_{CO_2}) it becomes necessary to consider the manner in which the levels of P_{CO_2} and $[H^+]$ may vary in different fluid compartments within the central nervous system. This will be the primary purpose of this discussion, which will be aided by employment of data concerning the nature of the respiratory response of normal men to increased tensions of inspired CO_2.

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RESPIRATORY RESPONSE TO LOW INSPIRED CONCENTRATIONS OF CARBON DIOXIDE (0 TO 6 PER CENT)

The respiratory response to CO_2 inhalation indicates the over-all reactivity of the mechanisms of respiratory control to deviations from their normal acid-base status. It is now customary when devising these "CO_2-sensitivity" curves to relate such changes in pulmonary ventilation or other measured variables to the induced increase in alveolar or blood P_{CO_2}. This conventional designation of alveolar or arterial P_{CO_2} as an index of the ultimate respiratory stimulus during CO_2 administration is useful for many purposes in physiological and pharmacological investigation. It is also an arbitrary index, since change in respiration during CO_2 breathing is correlated equally well with change in either P_{CO_2} or *p*H of fluids such as arterial blood, venous blood, cerebrospinal fluid, and even urine.

Normal Variation. The average respiratory response of 33 normal young men breathing various mixtures of CO_2 in 21 per cent O_2 in N_2 is shown in figure 1*A*, which was constructed by averaging control CO_2 sensitivity curves from several studies performed in this laboratory.[8–12] Figure 1*B*, based upon the same data, shows that the normal "average" CO_2 sensitivity curve of figure 1*A* is actually a deceptively smooth composite of an extreme range of variation in respiratory reactivity to change in alveolar P_{CO_2}. Normal reaction to CO_2 inhalation can be seen to vary from the 4 subjects selected to illustrate low "threshold" and high "sensitivity" through other groups representing more normal resting values but high or low sensitivity, to the subjects having high resting levels of P_{CO_2} and low reactivity to change in this stimulus index.

The variation in response of normal individuals to CO_2 has been previously de-

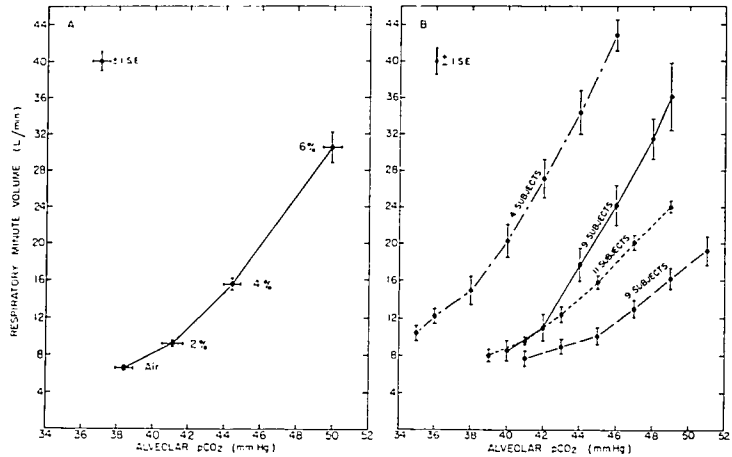

FIG. 1. Variability of the respiratory response of normal subjects to low concentrations of inspired carbon dioxide. In *A*, the responses to approximately 2, 4, and 6 per cent CO_2 in 21 per cent O_2 in N_2 are averaged. For *B*, the individual CO_2 "Response" curves were appraised to obtain interpolated values of respiratory minute volume at selected levels of P_{CO_2}.[2, 12] In the course of this appraisal, it became apparent that the total subject population could be grouped such that at least four statistically different patterns of respiratory response appeared.

scribed.[13] However no explanation exists for the extreme variability in response to P_{CO_2} shown by Schaefer [12] and by the subjects of figures 1*A* and *B*. Actually, an understanding of the basis for variability of respiratory response to CO_2 can hardly be expected when the mechanisms whereby CO_2 stimulates respiration are not known. For the present, it is worth noting that among normal young men there are those such as in group D of figure 1*B*, with a responsiveness to CO_2 no greater than has been described for elderly patients with chronic emphysema,[14] or for young men who have received large doses of meperidine.[9] Very likely such individuals are most susceptible to severe respiratory depression by narcotic agents, to hypoventilation during respiratory obstruction; and to hypercapnia during exercise.[7] This possibility should be further investigated.

Nature of the Average Carbon Dioxide Response Curve. The curves of figure 1A and *B* suggest also that the average respiratory minute volume response to increased alveolar P_{CO_2} follows a prominent and definable curve. However, since the sampling errors in the determination of alveolar P_{CO_2} by end-tidal methods are greatest at low tidal volumes, and errors should largely be those on the low side of mean alveolar P_{CO_2}, any tendency for curvature in the lower portions of the CO_2 sensitivity diagram will be erroneously emphasized by dilution of end-tidal samples with dead space gas. While these errors should not be large when ventilation exceeds resting values in a number of studies relating alveolar P_{CO_2} to ventilation no hint of curvature has been detected. As a result, the respiratory response to CO_2 breathing is most often considered to be essentially linear,[6, 15, 16] and special significance is attached by some investigators to an intercept P_{CO_2} (or apnea point) determined by downward extrapolation to zero ventilation.[5, 16]

Use of Arterial P_{CO_2}. For purposes such as studies of drug actions on respiration, the use of alveolar gas sampling for P_{CO_2} determination provides adequate information regarding

alteration of response to CO_2.[9] When, at considerable cost, determinations of respiratory reactivity to change in P_{CO_2} are somewhat improved by measuring P_{CO_2} in arterial blood,[5, 10, 17] the respiratory response to low concentrations of inspired CO_2 may still appear curvilinear in some subjects or subject groups but does not appear so in others (fig. 2). For this reason it is not now practical to define a uniformly applicable curve describing the relationship of respiratory minute volume to change in alveolar or arterial P_{CO_2}. Practically, it appears that the average response to change in P_{CO_2} may be considered nearly linear in the region of normal homeostasis,[6, 15-17] whether measurements of P_{CO_2} are made upon alveolar gas or arterial blood.

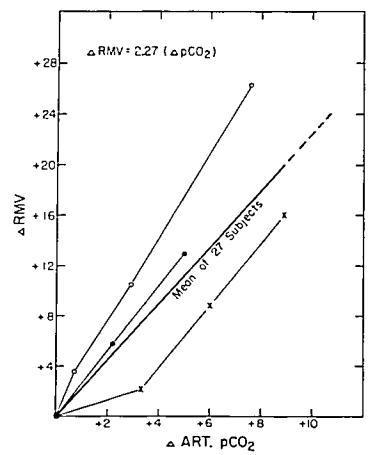

FIG. 2. Relationships of change in respiratory minute volume to change in the P_{CO_2} of arterial blood produced in groups of normal young men by administration of low concentrations of carbon dioxide. Each plotted point represents the mean of the subject group studied in the particular condition. ○ from reference 5; ×, reference 10; ●, reference 17. It should be noted that in the data of Lerche *et al.*,[5] the points in each case represent the average of three determinations on each of the 7 subjects and that the gas administered was CO_2 in 33 per cent O_2 rather than in 21 per cent O_2 in nitrogen. The line representing the regression of change in respiratory minute volume upon change in CO_2 tension in the 27 subjects was obtained from the mean rather than from individual values.

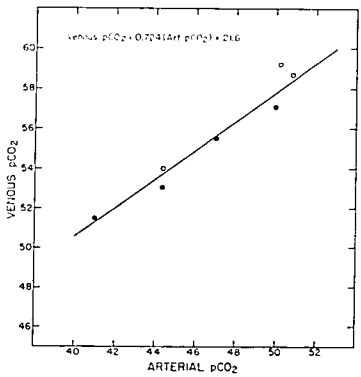

FIG. 3. Regression of the CO_2 tension of internal jugular venous P_{CO_2} upon that in arterial blood in normal subjects exposed to low concentrations of inspired CO_2 in 21 per cent O_2 in nitrogen. Plotted points represent mean values for the 8 and 5 subjects used in the several phases of the two studies selected. ● from reference 10; ○, reference 3. The somewhat smaller rise in central venous than in arterial P_{CO_2} is in large measure related to the influence of hypercapnia upon the rate of brain circulation.[10]

Relationships of Arterial to Internal Jugular Venous P_{CO_2}. There are situations in which change in the P_{CO_2} of arterial blood loses its normally considerable value as an index of the respiratory stimulus and measurement of change in central P_{CO_2} would be desirable. During inhalation of oxygen at supra-normal partial pressures, when tissue hypercapnia and arterial hypocapnia can be concurrent,[10] the lowered arterial P_{CO_2} merely reflects the influence of increased ventilation upon blood passing through the lungs. A similar dissociation of the P_{CO_2} of internal jugular venous and arterial blood has been shown for recovery from acute exposure to CO_2,[18] and possibly, may be a normal occurrence between arterial blood and the blood perfusing the respiratory centers in respiratory control at rest. It is not routinely convenient to sample internal jugular venous blood for measurement of its CO_2 tension and *p*H. An indication of the manner in which the brain venous P_{CO_2} is altered by breathing CO_2 can be seen in figure 3 which shows the relation-

ships of arterial and internal jugular venous P_{CO_2} in 13 subjects exposed to low concentrations of inspired CO_2. This figure, together with the data of figure 2, provide a close approximation to the interrelationships of respiration, arterial P_{CO_2}, and the internal jugular P_{CO_2} expected during CO_2 breathing in a group of normal young subjects and may be useful in estimating changes in one of these variables from changes in the others in large series of measurements.

For other purposes it is sometimes desirable to estimate the influence of CO_2 upon arterial or internal jugular venous *p*H. Figure 4, which summarizes the average relationships between blood P_{CO_2} and *p*H observed in several studies, is in fact a form of CO_2 dissociation curve.

Limitations of Brain Venous Blood P_{CO_2} and pH Measurements in Studies of Respiratory Control. While measurements of internal jugular venous blood may appear to provide a more generally useful index of the central levels of P_{CO_2} than does arterial blood, the composition of brain venous blood is, after all, the integrated result of temporal and spatial differences in the metabolism and circulation of all portions of the brain ultimately drained by the internal jugular veins. Centers concerned with respiration appear in rather

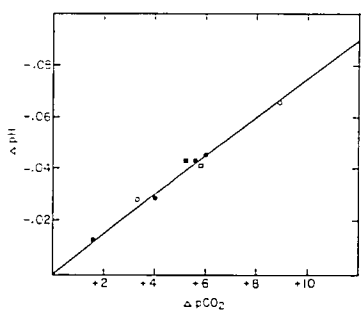

FIG. 4. Relationship of change in P_{CO_2} to change in *p*H in the arterial and internal jugular venous blood of normal subjects. Each plotted point represents the average finding in the 8 or 5 subjects used for the studies which provided the data.[3, 10] The observed slope of this relationship, $-.0075$ ΔpH/mm. Hg ΔP_{CO_2} is identical with that found in 7 other subjects by Loeschcke *et al.*[9] ○ = arterial.[10] ● = venous,[10] □ = arterial,[3] ■ = venous.[3]

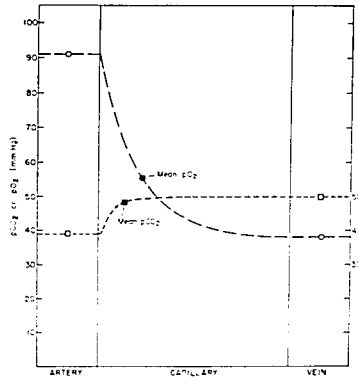

FIG. 5. Schema of pathways for change in gas tensions across the brain capillary bed. Graph represents diagrammatically measured values for the P_{CO_2} and P_{O_2} of arterial blood entering and leaving the brain capillary bed,[3] together with levels of mean capillary P_{O_2} and P_{CO_2} calculated as indicated in the text. The width of the portion of the graph labelled "capillary" indicates either capillary length or time spent by blood in the brain capillary. The term "mean" applies to the average value for the gas tension within the average of all brain capillaries.

widely separated parts of the brain, and while it has been shown that medullary vessels are responsive to increased P_{CO_2} in a manner qualitatively similar to those of the brain cortex,[19] is is not certain that the vessels supplying portions of the brain concerned with respiration respond to change in arterial P_{CO_2} in a manner quantitatively identical to the response of other brain vessels.[10] Even if the smooth muscle cells of all brain vessels do have quantitatively similar reactivity to change in P_{CO_2}, the usefulness of brain venous blood as a sole source of information concerning chemical factors is respiratory control will be limited since (1) it is not clear how the tension of CO_2 in either arterial or jugular venous blood relates to the average or mean brain capillary P_{CO_2}, and (2) there is now considerable likelihood that a part of the normal respiratory drive is related to acid-base changes paralleling those in cerebrospinal fluid and not necessarily related to changes in either arterial or central venous blood.[1, 3, 20-23] It will,

TABLE 1

Gas Breathed	Resp. Min. Vol. (L. minute, m.² BTPS)	Carbon Dioxide Tension (mm. Hg)		
		Arterial	Mean Capillary	Int. Jug. Venous
Air	3.07	41.0	?	51.5
4.3% CO_2	7.55	47.0	?	55.5
100% O_2*	4.08	33.8	?	53.9

* Mean of 15 and 30 minute exposures at 3.5 atms.

therefore, be necessary to pay attention to the possibility of determining the levels of P_{CO_2} and *p*H in these locations.

Mean Brain Capillary P_{CO_2}. The possibility exists that mean brain P_{CO_2} is more closely related to mean brain capillary P_{CO_2} than to the CO_2 tension in the blood leaving the brain capillaries to become internal jugular venous blood. Mean brain capillary P_{CO_2}, like mean brain capillary P_{O_2}, is a mathematical rather than a measureable physiological entity, since it represents the average P_{CO_2} in the average of all the brain capillaries. Figure 5, derived from data obtained by measurements upon arterial and internal jugular venous blood of normal young men breathing air while at rest at sea level, shows the probable average change in P_{O_2} across the brain capillary bed. The value for mean capillary P_{O_2} of about 55 mm. of mercury was determined by an integration procedure [24] based upon the assumption that, on the average for the entire brain, oxygen left the capillary at a uniform rate along the length of the capillary. Because of the characteristics of the hemoglobin dissociation curve, the mean P_{O_2} value appears under normal circumstances to be reached within the first fifth of the capillary length.

This approximation to an average gas tension in the brain capillary blood is even more difficult to justify for P_{CO_2} than for P_{O_2}. If CO_2 enters the blood from the brain at a rate which is uniform and, in the brain, equal to the rate of oxygen loss, the relatively linear characteristic of the CO_2 dissociation curve would require a nearly linear rise in P_{CO_2} across the brain capillary. In this case, mean brain capillary P_{CO_2} would approximate the arithmetical average of CO_2 tension in arterial and brain venous blood and be attained half way across the capillary bed. This is an unlikely possibility for several reasons. First, the gradient between tissue and blood should be highest near the arterial end of the capillary. Moreover, the very large amount of CO_2 contained in the highly buffered brain tissue (over 50 ml. of CO_2 per 100 Gm. of brain tissue) is in sharp contrast to the minute amount of extravascular oxygen in the brain (less than 0.1 ml. per 100 Gm. of brain tissue). With this reserve of CO_2 to maintain a diffusion gradient, the rapid diffusibility of CO_2 (over 20 times that of oxygen) should result in early elevation of the intracapillary P_{CO_2} to levels nearly as high as the ultimate venous CO_2 tension.[10] If this more likely possibility obtains, it could result from the rapid entrance of very small amounts of CO_2 into blood with still highly oxygenated (and hence more acid) hemoglobin in the first portion of the capillary bed. As illustrated by the postulated curve for change in P_{CO_2} in figure 5, the mean brain capillary P_{CO_2} would in this instance be attained early in the passage of blood through the capillary, and the P_{CO_2} of the largest proportion of brain tissue would be nearly as high as that in the venous blood.[10, 25–27]

Unfortunately, the *mean* P_{CO_2} of medullary, whole brain, or any other capillary blood is no more directly measureable than is its *mean* P_{O_2} (even with the oxygen electrode). A possible clue to aid in selection between the two possibilities presented may be offered by a study in which respiratory response to CO_2 and to O_2 were compared with the concurrent alterations of arterial and internal jugular venous P_{CO_2}.[10] In that study, oxygen caused arterial and jugular venous P_{CO_2} to change in opposite directions (table 1). This chemical bisection by oxygen permitted convenient separate appraisal of the relation of respiration to arterial and central venous levels of P_{CO_2} and, by this means, the effect of oxygen upon respiration was found to be slightly less than would have been expected from the rise in central venous P_{CO_2}.

It is now of interest to employ such data to estimate the relationship of mean brain capillary P_{CO_2} to the CO_2 tension of arterial and internal jugular venous blood. Two sets of

respiratory and blood gas data are available in table 1, one set for CO_2 inhalation, one for O_2 breathing. If oxygen does produce its slight respiratory stimulation by way of central accumulation of carbon dioxide and not through changes in sensitivity of the centers to chemical stimulation,[10] determination of the central P_{CO_2} level pertinent to respiratory stimulation by CO_2 should be possible, as follows:

Consider respiratory responsiveness or "sensitivity" to change in mean central P_{CO_2}, symbolized by a, to be the same during CO_2 and O_2 breathing. Then, during CO_2 administration,

$$a = \frac{RMV_{CO_2} - RMV_{air}}{\text{Mean } P_{CO_2 CO_2} - \text{Mean } P_{CO_2 air}}. \quad (1)$$

And, during O_2 breathing,

$$a = \frac{RMV_{O_2} - RMV_{air}}{\text{Mean } P_{CO_2 O_2} - \text{Mean } P_{CO_2 air}}. \quad (2)$$

In each instance the mean central P_{CO_2} can be indicated as

$$\text{Mean central } P_{CO_2} = \text{Venous } P_{CO_2} - \frac{(\text{Venous } P_{CO_2} - \text{Arterial } P_{CO_2})}{x}. \quad (3)$$

This expression is similar in principle to that in which Bareroft [28] described the approximate mean capillary P_{O_2} during air breathing as being equal to

$$\text{Venous } P_{O_2} + \frac{(\text{Arterial } P_{O_2} - \text{Venous } P_{O_2})}{3}.$$

Using the data for the two experimental conditions in table 1 (breathing CO_2 or O_2), equating expressions (1) and (2), and substituting expression (3) in the appropriate positions for mean central capillary P_{CO_2}, it is possible to solve for x and thereby obtain values for mean central capillary P_{CO_2} which may prove to relate to each other somewhat more closely in terms of change in respiratory stimulus indices than does the P_{CO_2} of either arterial or internal jugular venous blood. x is found to be 6.7, suggesting (1) that mean central capillary P_{CO_2} in the examples selected is only about $\frac{1}{7}$ of the Δ A-V P_{CO_2} less than the final venous value for P_{CO_2} and (2) that P_{CO_2} therefore does not increase at a uniform rate across the brain capillary (fig. 5). It must be kept in mind that the procedure illustrated for determining a value for mean central capillary P_{CO_2} is useful only insofar as no gross differences exist in the dynamics of P_{CO_2} equilibrium in the conditions employed. Differences may exist between the situations chosen, with mean capillary P_{CO_2} during CO_2 breathing most probably being closer to the venous value than would be the case for oxygen inhalation. On this basis it should still be reasonable to expect that the mean brain capillary P_{CO_2} (indicated by ? in table 1) would under ordinary circumstances be no further below the venous value than $\frac{1}{7}$ of the ΔP_{CO_2} between venous and arterial blood.

Cerebrospinal Fluid P_{CO_2}. Perhaps beginning with the demonstrations by Jacobs of free permeability of cell membranes to CO_2 and the relative impermeability to bicarbonate ion,[29] attention has been given to the possibility that changes in the acid-base composition of cerebrospinal and other intracranial extracellular fluid may have considerable relationship to respiratory control.[1, 3, 21-23, 29, 30] Several types of studies appear to bear directly upon this question, including (1) the demonstration by Leusen [30] and more precisely by Loeschcke *et al.*[21] and Mitchell *et al.*[22] that change in the *p*H of cerebrospinal fluid perfusing the fourth ventricle causes respiratory stimulation, (2) experiments which reconfirmed the slow entrance into cerebrospinal fluid of injected acid or alkali and demonstrated the dominant influence upon cerebrospinal fluid P_{CO_2} of ventilatory alterations in arterial P_{CO_2},[30] and (3) attempts at quantitative separation of the respective influences upon respiration of changes in the $[H^+]$ and P_{CO_2} of blood [5, 6, 15, 31, 32] and, more recently, in blood and cerebrospinal fluid.[3] For each of these types of investigation it has become important to determine the magnitude of changes in cerebrospinal fluid P_{CO_2} associated with carbon dioxide breathing and certain other forms of respiratory stimulation.

The entrance of fixed acid or base into the over-all cerebrospinal fluid compartment is a slow process.[33] Within a respiratory cycle, during the term of most CO_2 sensitivity studies and even over the period of most anesthetic procedures, detectable change in the $[HCO_3^-]$ of cerebrospinal fluid is unlikely.

Thus, as mentioned above, variations in the *p*H of cerebrospinal and, probably, other extracellular fluid of the central nervous system, are primarily dependent upon the physical factor of change in its P_{CO_2} rather than upon altered chemical composition.[30]

Unfortunately there is as yet no direct information from studies in animals or man regarding either the levels of P_{CO_2} in the cerebrospinal fluid or the dynamics of CO_2 exchange between blood and cerebrospinal fluid. Robin *et al.*[20] have shown that in steady states the P_{CO_2} in the cisternal cerebrospinal fluid of ten dogs averaged 6 mm. of mercury higher than that in simultaneously sampled arterial blood. This observation suggests that the average P_{CO_2} of intracranial cerebrospinal fluid in man may be close to that of internal jugular venous blood. This appears to be the case, and since the bicarbonate concentration of cerebrospinal fluid in resting man is about 2 m*M*/l. less than that of arterial blood, the *p*H of cerebrospinal fluid is normally more acid than that even of brain venous blood (Semple and associates, personal communicaiton). With regard to influences of cerebrospinal fluid composition in respiratory control, it will be necessary to learn whether important differences in the acid-base composition of cerebrospinal fluid exist among the several ventricles, as well as to compare the dynamics of change in the acid-base composition of cerebrospinal fluid and blood with the dynamics of changes in respiration.

Intracellular P_{CO_2}. Thus far, consideration has been given only to average changes in CO_2 tension in intracranial extracellular fluid compartments. There are, however, at least three distinct types of cells closely concerned with the influence of CO_2 upon respiration and in a single situation the levels of P_{CO_2} within each may be different. For example, the smooth muscle cells of brain vasculature, through their influence upon brain blood flow and rate of metabolite removal, contribute to determination of the central levels of CO_2 tension, and in turn, these cells are themselves grossly affected by P_{CO_2}. Regulation of brain vascular resistance through influence of CO_2 upon cerebral vascular smooth muscle appears dependent upon the level of P_{CO_2} rather than *p*H in the blood,[2, 3, 7] and moreover, upon changes in the level of P_{CO_2} reflected in the arterial rather than in the internal jugular venous blood.[7, 34] It remains unanswered whether the influence of P_{CO_2} upon these smooth muscle cells is mediated via alteration of intracellular *p*H or another effect of carbon dioxide.[3]

The second cell type to be considered includes the central neurons concerned at various sites with respiratory regulation. Again, these cells should be freely permeable to CO_2 and somehow responsive to change in the internal environmental level of CO_2. In this regard, Robin and Bromberg have recently stressed that cells of the central nervous system in reality have two forms of "internal milieu," including the chemical environment provided by the ambient extracellular fluids and the environment of the processes occurring in the fluids within the cell.[35] The levels of P_{CO_2} in these distinct extravascular fluid environments should be nearly identical and should considerably exceed the tensions of CO_2 in the arterial blood supplying the cells. Actually, certain of these chemoceptive cells, in particular those responsive to changes in cerebrospinal fluid *p*H, [20 22] may be influenced concurrently by the levels of P_{CO_2} in blood and cerebrospinal fluid,[3] and it is even probable that as an alteration of tissue P_{CO_2} occurs the changes in extra- and intracellular *p*H induced will be least proportional to each other. While it is usually considered that the ultimate influences upon respiration of CO_2 are those expressed *within* the cells concerned with respiratory regulation,[1] there is not as yet reason to believe that the central neurons react to intracellular rather than to extravascular, extracellular acid-base changes.[3]

The third cell type concerned with stimulation of respiration by CO_2 is the glomus cell of the carotid and aortic bodies. The details of the conflicting evidence regarding the reactivity of these structures to acid-base changes and their importance in respiratory control is summarized elsewhere.[23] Under normal circumstances, the carbon dioxide tension at and within the chemoreceptor cells, at least those of the carotid bodies, should essentially equal that in the arterial blood. This probably unique situation for functioning nerve cells is imposed by the extreme volume

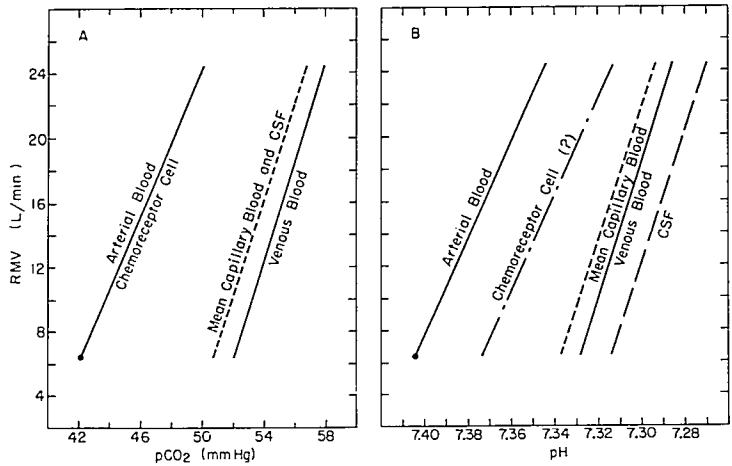

FIG. 6*A* and *B*. Relationship of respiratory minute volume to the P_{CO_2} and *p*H of various extra- and intracellular fluids during CO_2 inhalation. This diagram is based only in part upon empirical observations, and is offered as a composite illustration of probable changes in acid-base composition of the fluids concerned.

In *A*, the curve for arterial P_{CO_2} is transposed from figure 2. It ascends from the mean values for P_{CO_2} and RMV observed during air breathing in 21 subjects in whom resting values for both P_{CO_2} and *p*H are available.[2, 10] Respiratory relationships to venous P_{CO_2} are derived by using the regression of venous upon arterial P_{CO_2}, and to "mean brain capillary P_{CO_2}" by assuming P_{CO_2} values about one-seventh of the A-V $\triangle P_{CO_2}$ less than the venous value (see text).

In *B*, values relating respiration to arterial *p*H stem from the average arterial *p*H during air breathing in 21 subjects.[2, 10] Change in arterial and venous *p*H is based upon the *p*H/P_{CO_2} relationships of figure 4, and the regression of venous upon arterial P_{CO_2} in figure 3. Mean capillary *p*H is estimated as described for mean capillary P_{CO_2} in the text. Cerebrospinal fluid *p*H is approximated by calculations based upon a fixed bicarbonate concentration 1.6 mM/l. less than that in arterial blood during air breathing and an average P_{CO_2} equivalent to that proposed for mean capillary blood. The difference of 1.6 mM/l. between arterial and cerebrospinal fluid [HCO_3^-] is derived from data of Semple (personal communication).

rate of blood flow through the carotid bodies which cause the composition of venous blood draining these structures to be almost the same as that of the arterial blood supplying them.[36]

Interrelationships of P_{CO_2} to pH at Different Locations. Figures 6*A* and *B* summarize for CO_2 breathing the proposed average relationships between respiration and the P_{CO_2} and *p*H of arterial, mean brain capillary, and brain venous blood, peripheral chemoreceptor cells, cerebrospinal fluid, and central neurons. These relationships are, of course, purely descriptive, have no direct bearing upon ultimate mechanisms of respiratory regulation, and are shown to illustrate that "internal homeostasis," even when restricted to acute, respiratory regulation of acid-base balance, is a multiple phenomenon involving a number of separate levels of homeostasis.

SUMMARY

Undoubtedly, the response of the respiratory neurons to deviations in their local environment plays the dominant role in the total process responsible for acid-base and oxygen homeastasis. The amazing primary reactivity required for this system, and the coordinated stabilization of its remotely separated components, is dependent almost entirely upon the unique combination of physical and chemical

characteristics of the CO_2 produced by the cells of the same regulating system. However, in responding to local changes, the respiratory neurons cause alterations in the acid-base composition of arterial blood and other fluids which modify the local environments of many other cells. Only the small fraction of these cells showing intrinsic reactivity to acid-base change are capable of responding and, hence, acute active homeostatic regulation of the internal environment is restricted to the reactive cell types. These cells, including central respiratory neurons, vascular smooth muscle cells and chemoreceptor glomus cells, exist in their most stable states at entirely different acid-base levels and provide independent sensing components in the fluctuating, dynamic interaction of factors concerned with acute adjustment of the acid-base composition by the total respiratory control mechanism. Nonreactive cells are passively dependent upon adjustments by and for these reactive cells. In the active system, regulation at a number of different acid-base levels (figs. 6A and *B*) is interlocked in a series of self-stabilizing loops and to obtain quantitative information bearing upon these interrelationships it becomes necessary to consider not only the nature of chemical factors responsible for control of respiration and brain circulation, but the influence of changes in these factors at different locations.

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