ACCLIMATIZATION TO CARBON DIOXIDE

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IN their classic study of the composition of alveolar gas, Haldane and Priestley drew attention to the remarkable constancy of the alveolar carbon dioxide tension.[21] Although the percentage of CO_2 in their alveolar samples varied, the partial pressure of CO_2 remained constant at 40 mm. of mercury despite a two-fold variation in oxygen tension and barometric pressure (647 to 1,261 mm. of mercury) produced by their journeys to the top of 4,406 foot Ben Nevis, the highest mountain in Great Britain, to the bottom of a mine below sea level in Cornwall and to a compression chamber in a London hospital. Indeed, the constancy of the alveolar and arterial CO_2 tensions in normal sea level residents has come to be a prime example of the stability of the *milieu intérieur*.

If Haldane and Priestley had lived in a more mountainous region than Great Britain, they might have presented their findings with a slightly different emphasis. Such moderate changes in oxygen or barometric pressure do not immediately alter breathing and the alveolar CO_2 tension, but prolonged exposure to even moderate hypoxia produces chronic hypocapnia.[2] Eight years after their earlier study, Haldane and his associates travelled to the top of Pike's Peak, Colorado, where their alveolar CO_2 tensions were found to average 26 instead of 40 mm. of mercury.[13] During the same summer their associate, Mabel P. FitzGerald, in a classic study of the composition of alveolar gas in 134 residents of 12 communities in the Colorado Rockies at altitudes of 5,000 to 14,100 feet above sea level, found that the alveolar CO_2 tension seemed to fall linearly at the rate of about 4.2 mm. of mercury per 100 mm. mercury decrease in barometric pressure.[16] The subsequent half-century has brought few studies of comparable scope.[10, 23, 20]

Although the effect of altitude on alveolar and arterial CO_2 tension is generally known, a value of 40 mm. of mercury has come to be widely accepted as normal. Doubtless this reflects the fact that most of the world's leading medical centers are located close to sea level, although several million people in both hemispheres live permanently at altitudes high enough to affect their CO_2 tensions. It is amusing to speculate how different our ideas of normal might be if the world had come to be intellectually dominated by the descendants of the Inca civilization, based in Cuzco at 11,440 feet, instead of the descendants of the earlier but hardly more extensive Roman civilization of the European lowlands. For convenience, usual sea level values will be considered normal in this review, but it should be recognized that an alveolar CO_2 tension of 33 mm. of mercury in a resident of Denver, Colorado,[2] or even of 29 mm. of mercury in a resident of Morococha, Peru,[10] is not inherently more abnormal than a value of 40 mm. of mercury in a resident of Oxford.

For the purposes of this review, acclimatization to CO_2 is interpreted to refer to changes of an adaptive nature produced and maintained as a result of deviations from the normal arterial CO_2 tension which have persisted at least for days and preferably much longer. The bulk of the literature dealing with the effects of hyperventilation, ably reviewed by Brown [7] a few years ago, and with acute respiratory acidosis, are therefore beyond the scope of this review. Because of the paucity of truly chronic experimental studies on acclimatization to altered CO_2 tensions alone, most of the discussion will deal with normal subjects residing at or acclimatizing to high altitude who exhibit hypocapnia, and patients with pulmonary emphysema who exhibit hypercapnia. For general information about these two groups, the reader is referred to recent reviews.[3, 28] The aspects of CO_2 acclimatization to be considered at most length concern the alterations in the ventilatory response to CO_2 and in the acid-base balance.

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Relation of Alveolar Carbon Dioxide to Ventilation and Metabolism

Obviously the stability of the normal alveolar CO_2 tension is a natural consequence of the virtual absence of CO_2 from the atmosphere and the precise adjustment of breathing to match the metabolic production of CO_2. With the exception of unusual situations in which the inspired CO_2 is not negligible, all persistent abnormalities in alveolar CO_2 tension come about because of changes in the ratio of alveolar ventilation to metabolic rate. This is true not only in normal subjects and hypercapnic patients at sea level but also in persons living at different altitudes.

In the steady state, the CO_2 eliminated by alveolar ventilation must just equal the CO_2 produced by metabolism ($\dot{V}_{CO_2}$ in ml./minute STPD). The ambient barometric pressure affects the relation between the per cent CO_2 in alveolar gas and its partial pressure ($P_{A_{CO_2}}$ in mm. of mercury). It also affects the relation between the actual volume of the alveolar ventilation ($\dot{V}_A$ in l./minute BTPS) and the number of gas molecules moved. In the derivation of the theoretical relationship among these parameters,[32] ambient barometric pressure completely cancels out. Thus, regardless of altitude or barometric pressure, $P_{A_{CO_2}}$ equals 0.863 $\dot{V}_{CO_2}$ divided by $\dot{V}_A$ in the steady state when inspired carbon dioxide is negligible. Because the metabolic rate is unaffected by altitude,[28] the alveolar CO_2 tension would remain unchanged if a person moved from one altitude to another without altering his depth or frequency of breathing movements.

Thus the hypocapnia of altitude residents indicates chronic hyperventilation and directs attention to the regulatory mechanisms governing their breathing. To anticipate, their hyperventilation seems to result in large part from acclimatization to chronic hypocapnia, an adaptation which helps to minimize their hypoxia.

Acclimatization of the Respiratory Center to Hypocapnia

Criteria for Evaluation. In evaluating the ventilatory response to CO_2 in individuals whose initial alveolar CO_2 tension is abnormal, it is important to decide whether to compare

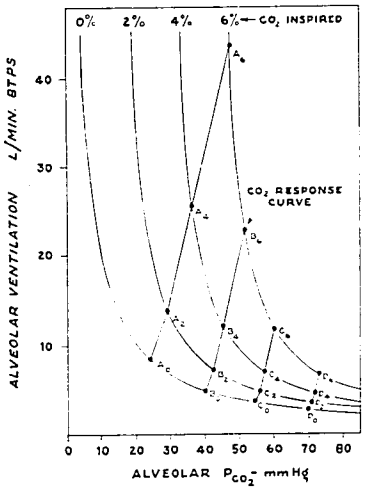

Fig. 1. Hypothetical carbon dioxide response curves of equal slope but different position, superimposed on theoretical ventilation lines. Despite their equal "sensitivity," inspired carbon dioxide would increase breathing more in persons whose initial alveolar carbon dioxide is lower. See text for assumptions.

ventilatory responses in terms of the per cent CO_2 administered or in terms of the change in alveolar and arterial CO_2 tensions that result. The distinction is important because one can predict from theoretical consideration that the increase in breathing of a hypercapnic subject will be less than that of a hypocapnic subject when each breathes the same CO_2 mixture even if their respiratory centers and peripheral response mechanisms are equally sensitive to elevation of arterial CO_2 tension.

Figure 1 shows why this is so. The hyperbolic lines in this figure have been drawn from the theoretical steady-state equation, referred to in the previous section, for an individual with an arbitrarily chosen rate of metabolism and (for simplicity) a respiratory quotient of unity.[32] Changes in these assumptions would not alter the conclusion to be drawn. Although all points on these curves satisfy the theoretical equation, when a normal individual is left to his own unconscious ho-

meostatic mechanisms he tends to stabilize his alveolar CO_2 tension at a particular point on each of these steady-state curves. In a normal person breathing air at sea level, for instance, the resting alveolar CO_2 tension might be at point B_0 in the figure, because only at that point would the stimulus to breathe derived from his arterial CO_2 tension provide the ventilation which would just eliminate the CO_2 being produced by his metabolism. When caused to breathe the indicated CO_2 mixtures, his points of stabilization are at progressively higher points of ventilation and alveolar CO_2 tension, represented by the successive intersections up to B_5. The line connecting these points thus reflects the respiratory stimulation produced by progressive increase in the alveolar and arterial CO_2 tensions and is termed a CO_2 response curve. Similar curves drawn with the total respiratory minute volume uncorrected for dead space, instead of alveolar ventilation, as ordinates are also referred to as CO_2 response curves. Such response curves evaluate neither the input nor the output of the respiratory center directly, but they are probably as close to a representation of its response as it is feasible to obtain at present. The slope of the response curve, the increment in ventilation produced per millimeter of mercury increase in alveolar or arterial CO_2 tension, serves as a measure of the sensitivity of the regulatory mechanisms. It should be recognized that this puts a rather narrow definition on sensitivity, which is inadequate to define the response of the system.[24]

In figure 1, lines of similar slope representing similar sensitivity have been drawn for hypothetical subjects who are hypocapnic or hypercapnic. It is immediately apparent that the hypocapnic individual *A* has a much larger increase in ventilation when breathing 6 per cent CO_2 than does the most hypercapnic individual *D*. The responses of the four hypothetical subjects would appear different even if they were expressed as precentage increases over resting ventilation. The apparent differences in response arise because any given inspired carbon dioxide tension produces a relatively large rise in the alveolar carbon dioxide tension of a hypocapnic individual, a rise which takes a very large increase in ventilation to balance, whereas a hypercapnic individual minimizes the rise in his alveolar CO_2 with a relatively slight change in his ventilation, because his carbon dioxide tension is already high. This point has frequently been overlooked.

Although the hypothetical individuals *A* through *D* in the figure have been assumed to have identical sensitivity to carbon dioxide, they differ widely in the actual alveolar carbon dioxide tension required to stimulate breathing to any given degree. How should this difference be described? Although one may presume that such a difference in the absolute position of CO_2 response curves represents a difference in the threshold for CO_2, evidence of a real threshold is usually lacking. The author feels it is safest to describe the position of the CO_2 response curve simply in terms of shifts to the right or left. In the adaptations to be discussed, such shifts are frequently much more striking than concomitant changes in slope or sensitivity. It seems reasonable to suppose that shifts in position are more likely to represent changes in the setting of the respiratory chemostat, whereas changes in slope are more likely to represent alterations in the amplitude of the response. The distinction, a speculative one, would be comparable to resetting the home thermostat versus increasing the size of the furnace.

Carbon Dioxide Response Curves at Altitude. When looked at from this standpoint, the CO_2 response curves of chronically hypocapnic residents of high altitudes are far to the left of normal sea level residents. The first indication of this came from the observations of Hasselbalch and Lindhard, who in 1911 measured their respiratory response to CO_2 during a 17 day sojourn in the Alps.[22] Their results suggested an altered respiratory response to CO_2 but did not define it. Because hypoxia stimulates breathing and itself seems to potentiate the stimulatory effects of elevated CO_2, even in sea level residents exposed acutely,[28] careful CO_2 response curves have been measured in the presence of added oxygen to eliminate hypoxic drive during the tests. Rahn and his associates measured three points on the CO_2 response curves of four subjects at Rochester, New York, 550 feet above sea level, and again during a sojourn on Mt.

Evans, Colorado, 14,100 feet above sea level.[21] The average CO_2 response curve was displaced about 10 mm. of mercury to the left during the week on Mt. Evans, and the slope of the line was slightly increased, representing increased sensitivity as well. Their resting alveolar CO_2 tensions on Mt. Evans breathing air averaged 28 mm. of mercury, compared to 40 mm. of mercury in Rochester. Similar results have been obtained by others,[24-26] and suggest that the respiratory center has acclimatized in such a way that it responds to deviations from the CO_2 tension to which it has become accustomed.

Genesis of Altitude Hypocapnia. How does the chronic hyperventilation of altitude residents come about in the first place? Undoubtedly the initial increase in breathing is produced by hypoxic stimulation of the carotid and aortic chemoreceptors. The ventilatory response to this hypoxic drive is relatively small at first because it produces hypocapnia which tends to reduce the normal CO_2 stimulus. It is believed that the CO_2 stimulus is restored by acclimatization of the respiratory center to the hypocapnia. This shifts the CO_2 response curve to the left, augmenting the breathing which lowers the CO_2 tension still further. Thus with progressive acclimatization the CO_2 response curve shifts far to the left and the ventilation is increased sufficiently to play an important role in minimizing hypoxia. As Dejours has shown most clearly in his review,[11] hypoxic drive continues to exert an effect on breathing; but when hypoxia is interrupted, breathing decreases only slightly (after a larger fall that is very transient) because CO_2 continues to be regulated at a low tension.

Studies at the White Mountain Research Station in California have shown the relative magnitude of the effects of acute hypoxia and chronic adaptations in resetting the CO_2 regulators.[24] Carbon dioxide response tests were carried out repeatedly in normal subjects at sea level and during sojourns of two to six weeks at 14,250 feet. During administration of the CO_2 the alveolar oxygen was monitored, and the oxygen concentration of the CO_2 mixture was continually adjusted to maintain the alveolar oxygen tension constant either at its normal sea level value of 100 mm. of mercury or its normal White Mountain value of 55 mm. of mercury regardless of the actual altitude. Such acute hypoxia during the tests at sea level shifted the CO_2 response curve about 1 to 3 mm. of mercury to the left, in agreement with the previous observations of Nielsen and Smith.[28] During residence at altitude, similar adjustment of the alveolar oxygen tension during the tests altered the CO_2 response curves similarly by about 1 to 3 mm. of mercury, but each of the curves was about 13 mm. of mercury to the left of the corresponding curve at sea level. In other words, the persistent shift in CO_2 response due to acclimatization was several times as large as the immediate effect produced by acute hypoxia.

This readjustment of the CO_2 response curve with altitude acclimatization appears to be a true case of acclimatization to chronic hypocapnia rather than a direct effect of hypoxia *per se*. Gilfillan and his associates have been studying the CO_2 response during altitude acclimatization of intact dogs and dogs whose carotid and aortic chemoreceptors had been surgically removed.[19] The normal dogs (and one dog which showed a respiratory response to cyanide injection after surgery) hyperventilated at altitude, developed hypocapnia, and showed a shift to the left in CO_2 response. The successfully glomectomized dogs, however, did not hyperventilate and were therefore even more hypoxic at altitude, developing extreme polycythemia. Nevertheless, throughout several months at 12,500 feet their CO_2 response curves did not change from what they had been at sea level. These results are what one would expect by extrapolation in time from the more clear-cut experiments of Brown and his associates.[5] They hyperventilated normal human subjects in a mechanical respirator for 24 hours without hypoxia and then measured the response to CO_2. The results indicated that the respiratory center had already begun to acclimatize to the hypocapnia, confirming the view that concurrent hypoxia is not an essential part of the CO_2 acclimatization picture.

Acclimatization of the Respiratory Center to Hypercapnia

There is relatively little published material on acclimatization to hypercapnia uncompli-

cated by hypoxia or disease processes. Perhaps the clearest observations on man are those reported by Schäfer.[35] Normal subjects were exposed for 8 days to an atmosphere of 3 per cent CO_2. This raised the alveolar CO_2 tension by 2 or 3 mm. of mercury and shifted the CO_2 response curve slightly to the right.

The relatively striking examples of acclimatization to hypercapnia are complicated by disease processes, particularly pulmonary emphysema, and by hypoxia. Concurrent hypoxia appears to have a small effect on the position of the CO_2 response curve in these patients[34] that is quite comparable to its effect in altitude residents. Several studies have been marred by the failure to evaluate the ventilatory response in terms of the CO_2 tension of the arterial blood (alveolar gas is obviously unsatisfactory here) rather than of the inspired gas. Nevertheless, it seems quite clear that the response curve is shifted to the right in many of the patients with chronic CO_2 retention, and that its slope is markedly reduced.[1, 3, 15, 29, 34] The shift to the right in chronic hypercapnia is in the opposite direction from that observed in chronic altitude hypocapnia, providing further support for the idea that both shifts represent acclimatization to the prevailing CO_2 tension in the body rather than to an effect of hypoxia *per se*.

There is admittedly some question concerning the proper interpretation of the altered CO_2 response of emphysematous patients because of the direct role that their abnormal pulmonary mechanics may play. It has been argued that the altered CO_2 response can be simulated in normal subjects by inserting an artificial resistance in the airway.[8, 14] This certainly diminishes the slope of the CO_2 response curve,[14] but the shift of the curve to the right is not so striking in these experiments. Perhaps that is too much to expect. Currently, the best evidence that adaptation of the respiratory center itself is not the major factor in every case comes from consideration of the work input and energy cost of breathing. These have been evaluated from measurements of the respiratory mechanics and the oxygen cost of increased breathing movements. The efforts of the respiratory muscles evaluated in these two ways appear to rise in some patients as much as in normal controls per millimeter of mercury rise in arterial CO_2 tension, although the ventilatory movement produced by these efforts is much less in the patients.[15, 34] Such observations strongly suggest that the amplitude of the response has been mechanically diminished, rather than that the respiratory centers of these patients has acclimatized to a different stimulus level.

On the other hand, in patients with a diminished response to 5 per cent CO_2, ventilation was increased two and three times as much during mild exercise and voluntary hyperventilation respectively, suggesting at least that the ventilatory response is not always limited solely by the maximum breathing capacity.[1] Moreover, Boutourline-Young and Whittenberger have reported success in restoring more normal CO_2 response in one patient by prolonged hyperventilation in a mechanical respirator, suggesting that at least in this case reversible acclimatization to hypercapnia may have been involved.[4] The question is still controversial.

Perhaps the problem can profitably be compared to that encountered in studying altitude acclimatization. Presumably mechanical factors are primary in emphysema, leading to the development of hypercapnia in the first place, just as hypoxic drive is primary in the genesis of altitude hypocapnia. Mechanical factors can act directly to push the CO_2 response in one direction, just as hypoxia itself can push the response in the other. Yet in the case of altitude, when hypoxic drive was interrupted, the contribution of respiratory acclimatization to hypocapnia became clear. The comparable experiment has not been accomplished in emphysema and appears impossible at present. By analogy, however, one wonders if direct mechanical factors and acclimatization may not both be involved, perhaps to varying degrees in different patients.

Time-Course of Respiratory Acclimatization to Carbon Dioxide

The respiratory center appears to begin acclimatizing to altered CO_2 tensions quite rapidly. A shift of the CO_2 response curve to the right was evident after only 3 days in an atmosphere of 3 per cent CO_2.[35] Evidence of a shift to the left was observed after only 24 hours of mechanical hyperventilation.[5]

The most extensive and prolonged studies, however, have been carried out at altitude. Earlier observations on the progressive fall in resting alveolar CO_2 tension during altitude acclimatization, which presumably reflects shift of at least the lower end of the CO_2 response curve,[20] have been confirmed by repeated measurements of CO_2 response curves.[9, 24-26] The adaptation begins in the first few hours, reaches the half-way point in perhaps half a day, and reaches a plateau in 2 to 5 days depending upon the subject. Observations for as long as six weeks show only slight further drifts, of the order of 2 or 3 mm. of mercury. On return of sojourners to sea level, the CO_2 response curve begins to shift back equally promptly, but may take a month or more to return completely to its pre-altitude position,[26, 33] in agreement with the early observation of Schneider that a man continued to hyperventilate for a month or more after return from a sojourn on Pike's peak.[36]

Possibly, when residence at altitude is prolonged for many years or generations, the CO_2 response curve may shift back slightly from its extreme left-hand position. Chiodi has reported that Caucasian newcomers to Mina Aguilar in the Argentine Andes hyperventilate more and have lower arterial CO_2 tensions in the first few weeks than the Andean Indians who have lived there for many years.[9] Measurements at the 13,090 foot level indicated that the CO_2 response curves of the newcomers were further to the left than those of the long-term residents at that altitude. Unfortunately, the possibility of individual or racial differences is very difficult to rule out.

Tissue Changes in Carbon Dioxide Acclimatization

The best-known biochemical changes observed with chronic alterations in the arterial carbon dioxide tension are the changes in the acid-base balance of the blood initiated via the respiratory route but greatly modified by the action of the kidneys. Indeed, they are so well known that they need relatively little comment here. When alveolar CO_2 tension is first reduced by hyperventilation, CO_2 is drawn out of the blood and other fluids, reducing the concentrations of carbonic acid and bicarbonate as well. The effect of carbon dioxide on the kidney is the subject of another paper in this symposium. Suffice it to say here that despite the fall in concentration of bicarbonate ions in the plasma and presumably in the glomerular filtrate, tubular reabsorption of sodium bicarbonate falls still further, probably because of the altered tissue CO_2 tension, so that sodium bicarbonate excretion increases and the urinary pH tends to rise. The net effect is a further decrease in the bicarbonate concentration of the plasma and a tendency for the arterial pH to return toward normal. Converse changes occur in respiratory acidosis, with a further rise in bicarbonate concentration and again a tendency for arterial pH to return toward normal.[6, 20, 39]

In long-term residents of high altitudes, these processes have had time to complete the adjustment. The arterial pH is entirely normal,[9, 12] indicating complete renal compensation. The early studies of Dill and his associates still provide the most extensive picture of the blood chemistry over a wide range of altitudes.[12] In general, the decreased plasma bicarbonate was reflected in approximately equal shares by an increase in chloride and a decrease in sodium concentrations. Patients with CO_2 retention are more difficult to evaluate because their disease processes are not necessarily stable. Some show very severe acidosis with arterial pH values even below 7.0,[37] whereas in other series the renal compensation appears to have been better or the disease is milder.[1]

Because of the long cherished hypothesis that CO_2 stimulates respiration by virtue of its ability to lower the pH,[41] one is tempted to try to explain the shifts in CO_2 response curves in terms of shifts in the relation between CO_2 tension and pH brought about by the renal compensatory mechanism. Measurement of intracellular pH in the important receptor cells appears to be impossible with current techniques, but one might reasonably presume that renal compensation would affect the acid-base balance of the blood before it affected that of intracellular fluid. In altitude acclimatization, however, the CO_2 response curve shifts faster than the development of renal acid-base compensation, so that the arterial pH may remain slightly alkaline for several days or a few weeks.[9, 26] Measurement of arterial pH dur-

ing determination of the CO_2 response curves showed that CO_2 was stimulating breathing when the arterial *p*H was still appreciably more alkaline than at sea level.[16] Conversely, attempts to explain the diminished CO_2 response of emphysematous patients in terms of their acid-base status proved unsuccessful.[1] An attempt to improve the CO_2 response of patients by decreasing their arterial bicarbonate also proved disappointing.[15]

The CO_2 stores of the body are the subject of another paper in this symposium. Suffice it to say here that they are remarkably large, extending far beyond the dissolved CO_2 and bicarbonate of extracellular fluid.[17, 27] When the alveolar CO_2 tension is acutely changed, therefore, although a sufficiently steady state for respiratory response measurements is reached within 5 to 10 minutes, the tissues probably do not come into complete equilibrium for days.[27] The renal compensations are also very slow, as noted above. For this reason, it is unsafe to presume that changes occurring in the first few hours of hypocapnia or hypercapnia resemble the long-term adjustments of true acclimatization. Transient alterations in respiratory exchange ratio, urinary composition, and arterial *p*H, for example, do not persist into the truly acclimatized state.

When one surveys the literature of this field, one is particularly impressed by two facts: how little evidence is available on truly long-term acclimatization to altered carbon dioxide tensions uncomplicated by hypoxia or disease; and how little the normal physiology is upset by chronic "abnormalities" in CO_2 tension below the frankly narcotic level, even despite concomitant hypoxia, once renal compensation has returned the arterial *p*H to normal.

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