# THE EFFECT OF DRUGS ON THE RESPIRATORY RESPONSE TO CARBON DIOXIDE

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## General Considerations

There are many methods of studying the effects of drugs on respiration and all of them have their limitations. At the present time the respiratory response to carbon dioxide appears to be the most useful, but even here there are a variety of techniques with varying degrees of accuracy and usefulness. Respiratory measurements have been expressed in terms of respiratory rate, minute volume, alveolar ventilation and ventilation ratio. The change in brain tissue $P_{CO_2}$ which directly and indirectly brings about the change in respiration has been approximated by the arterial blood $P_{CO_2}$, the internal jugular vein blood $P_{CO_2}$, the alveolar $P_{CO_2}$, or by simply stating the concentration of inhaled carbon dioxide. Stimulus response curves, *i.e.*, plots of a respiratory measurement versus an index of brain tissue $P_{CO_2}$, give the most accurate appraisal of the effect of drugs on respiration.

### Ventilation Measurements

*Respiratory Rate.* Perhaps the simplest method of assaying respiratory stimulation or depression would be to observe respiratory rate or frequency. However, shallow rapid breathing may not be as efficient as slow deep breathing so that changes in frequency may lead to confusing and erroneous results. Moreover, significant effects may be overlooked with this insensitive method. Even when respiratory rate is plotted versus $P_{CO_2}$ the measurements are still relatively insensitive.[1]

*Minute Volume or Alveolar Ventilation.* Measurements of minute volume or alveolar ventilation alone in the subject breathing room air without concommitant measurements or approximations of tissue $CO_2$ concentrations suffer from the primary disadvantage of being insensitive. In addition they have the obvious defect that metabolic effects may be misinterpreted as respiratory effects. This is readily apparent on inspection of figure 1. (Parallel displacement of a response curve constitutes respiratory stimulation or depression and it may be accompanied by only slight changes in ventilation since one must stay on an iso-$CO_2$ excretion line.)

Of the various combinations of respiratory measurements and approximations of tissue $CO_2$ concentration we prefer a plot of alveolar ventilation versus alveolar $P_{CO_2}$ concentration. The reason for this preference is that the corrected product of these two terms is the $CO_2$ excretion rate and this makes it simpler to understand some of the necessary interrelation-

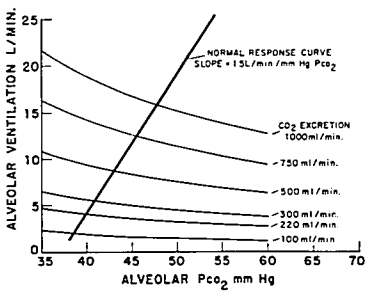


Fig. 1. Alveolar ventilation-alveolar $P_{CO_2}$ response curve. Points to the right of the response curve represent respiratory depression while those to the left represent respiratory stimulation. The product of alveolar ventilation and alveolar $P_{CO_2}$ represents a $CO_2$ excretion rate which can be expressed as ml./minute of dry gas at 37 C. and 760 mm. of mercury after appropriate corrections are made. The lighter lines indicate constant $CO_2$ output rates. These $CO_2$ isopleths are for *total* $CO_2$ output per minute regardless of whether this output is all endogenous excretion or is in part due to inhaled carbon dioxide. If $CO_2$ output is put on an axis perpendicular to the plane of the paper this figure can be converted to a three dimensional surface. Figure 4 is then another orthographic view of this surface.

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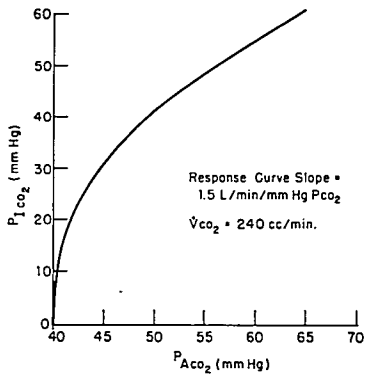


FIG. 2. The theoretical relationship between the partial pressure of $CO_2$ in the inhaled air and in the alveolar gas under conditions of constant net $CO_2$ excretion. This curve was plotted by assuming a respiratory response curve slope of 1.5 l./minute/mm. Hg $P_{CO_2}$ and a $CO_2$ excretion of 240 ml./minute.

ships between ventilation, $CO_2$ excretion and $P_{CO_2}$. Minute volume is preferred to alveolar ventilation by some because it is easier to measure; one does not have to worry about dead space and how dead space varies with ventilation. When the computation of alveolar ventilation can be done automatically [2] this argument in favor of minute volume disappears. It is also preferred by some because it more closely represents the output of the respiratory center than does alveolar ventilation. This advantage does not appear to us to outweigh the advantages of a plot of alveolar ventilation versus $P_{CO_2}$. Moreover, minute volume is not a perfect representation of the output (efferent phrenic nerve potentials would be better). For the pragmatic purpose of comparing the effects of drugs on respiration either minute volume or alveolar ventilation is capable of giving equally good results.

*Ventilation Ratio.* The ventilation ratio, the ratio of any given ventilation to that in the resting state, has been used by some in an attempt to make the slope of the ventilation-$P_{CO_2}$ response curve independent of body size. The use of ventilation ratio accomplishes the same thing as expressing ventilation in terms of volume per minute per square meter of surface area. Either expression, ventilation ratio or l./minute/m.$^2$ carries with it the reasonable but unproven assumption that ventilation at elevated $CO_2$ concentrations is proportional to body surface area. In addition to making use of an unproven assumption, ventilation ratios may introduce further error into the ventilation measurement. The resting ventilation measurements are subject to errors. When the actual ventilation measurement is divided by these terms further error is introduced into the final data. Of course, nothing is lost by dividing by a constant but if the resting ventilation each day is used the precision of the data may decrease. Since the ventilation-$P_{CO_2}$ response curves slopes vary substantially from subject to subject who are the same size, there does not appear to be any great gain in uniformity by compensating for differences in body size. As long as cross-over comparisons of the effects of drugs are made in the same individual nothing is gained in statistical precision by use of the ventilation ratio.

## $P_{CO_2}$ Measurements

*Alveolar and Arterial $P_{CO_2}$.* The end-expiratory $P_{CO_2}$ is the simplest and easiest $P_{CO_2}$ measurement to determine either electronically,[2] electromechanically,[3] or mechanically.[4] Arterial $P_{CO_2}$ closely follows the alveolar [5, 6] and in the normal subject there appears to be no gain in using the former in preference to the latter.

*Internal Jugular $P_{CO_2}$.* Internal jugular vein $P_{CO_2}$ may give a better index of brain tissue $P_{CO_2}$ than arterial $P_{CO_2}$.[7] However, it is considerably more difficult to obtain and this limits its usefulness for drug studies, particularly repeated studies in the same individual. Indeed, in one recent study there was a 40 per cent loss of data with this method due to technical difficulties.[8] It may be that the arterial blood $P_{CO_2}$ is a better index of respiratory center $P_{CO_2}$ since there is evidence to suggest that blood flow through this area of the brain may be more rapid than through the brain as a whole.[9] The fact that plots of internal jugular vein blood $P_{CO_2}$ versus ventilation are linear whereas those of alveolar $P_{CO_2}$ are not under conditions of rapidly changing $P_{CO_2}$ levels may be solely due to the fortuitous concurrence of two compensating

errors: (1) a lag between internal jugular vein $P_{CO_2}$ and brain tissue $P_{CO_2}$ due to a filling or emptying of brain tissue compartment with $CO_2$ and (2) a change in cerebral blood flow due to a change in $P_{CO_2}$. For the practical purpose of comparing drugs such errors as might be introduced by the use of alveolar $P_{CO_2}$ instead of internal jugular vein blood $P_{CO_2}$ tend to cancel out.

*Inhaled $CO_2$ Concentration.* A simple statement of the concentration of inhaled carbon dioxide tends to specify the alveolar $P_{CO_2}$ concentrations (fig. 2). Hence, a plot of ventilation against inhaled carbon dioxide concentration can be converted to a plot of ventilation versus alveolar $P_{CO_2}$ provided the individual's resting carbon dioxide production rate and response curve slope is known and the appropriate compensations for storage effects and increased production due to the increased exercise accompanying the increased ventilation are made. In general, it is better to avoid the assumptions contained in the foregoing, but it is well to appreciate that a plot of minute volume versus inhaled $CO_2$ concentration such as was done in 1890 by Loewe [10] is not far removed from response curves of today.

## Respiratory Response Curve

*Methods of Elevating Body $P_{CO_2}$.* The three principal methods of elevating body $P_{CO_2}$ levels are (1) continuous steady increase in $P_{CO_2}$ as by rebreathing techniques,[11, 12] (2) elevation of $P_{CO_2}$ in discrete steps by breathing gas of constant $CO_2$ content for protracted periods of time [10, 13] and (3) maintenance of ventilation at a constant elevated value by continuous servo controlled variations in $CO_2$ content of inhaled gas.[14]

We prefer the rebreathing technique because it permits the rapid attainment of elevated $P_{CO_2}$ levels with a minimum of subject discomfort, it gives a continuous plot of the data, it is easy to perform, and it may be repeated at frequent intervals. It has the theoretical disadvantage that equilibrium conditions are not employed; hence the measured response curve may be slightly displaced towards higher values of $P_{CO_2}$, and it may have a slightly flatter slope than the true equilibrium curve. However, a practical equilibrium is reached,[15] and any differences between the actual and theoretical curve tend to cancel when comparisons of drugs are made in the same individual.

The main disadvantage of the inhalation of fixed $CO_2$ concentrations and of the continuous servo-control of inhaled $CO_2$ content is that marked discomfort is produced at very elevated $P_{CO_2}$ levels. The latter is the worst in this regard—subjects cannot tolerate an elevation of $P_{CO_2}$ of over 3 mm. of mercury for more than an hour. This, by the way, is the amount of elevation expected from inhaling 3.3 per cent $CO_2$. The shorter exposure period involved in inhaling discrete concentrations raises the tolerance limit of inhaled carbon dioxide, but the tolerance may still not permit sufficient elevation of $P_{CO_2}$ to obtain a true picture of drug effects.

*Advantages of Achieving High Values of $P_{CO_2}$.* (1) Some drugs, the narcotics in particular, appear to produce a parallel displacement of the ventilation-$P_{CO_2}$ response curve, but only at elevated levels of $P_{CO_2}$. At lower levels, near normal, the response curve after drug approaches that of the control curve.[1] This can readily be appreciated on examining figure 3.[16]

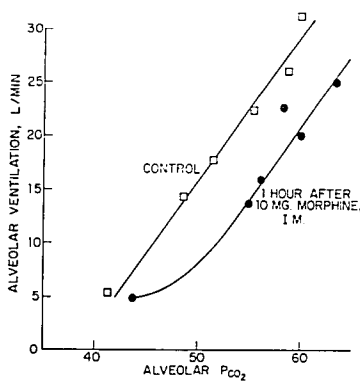


Fig. 3. Respiratory response curves obtained before and one hour after 10 mg. morphine sulfate intramuscularly. The end-expiratory $P_{CO_2}$ is plotted against the alveolar ventilation.[15]

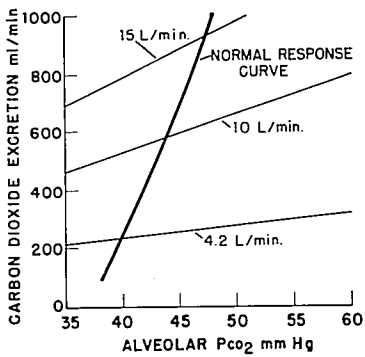


FIG. 4. Carbon dioxide excretion-alveolar $P_{CO_2}$ response curve. Figure 4 is another orthographic projection of the surface pictured in figure 1. Instead of $CO_2$ isopleths this figure contains ventilation isopleths. If there is an increase in $CO_2$ production the alveolar $P_{CO_2}$ must rise along the response curve unless there is secondary respiratory stimulation or depression. The response curve shown as a heavy black line is the same one shown in figure 1. Points to the left of the response curve represent respiratory stimulation while those to the right represent respiratory depression.

(2) As will be discussed later, parallel displacement of the response curve is more meaningful in terms of effects on the respiratory center than changes in slope, and a parallel displacement is most apt to be seen at the higher $P_{CO_2}$ levels.

(3) The use of multiple levels enables several estimates of the effect to be made rather than just one thereby increasing the statistical precision with which the effect is measured.

(4) The measurements of ventilation and alveolar $P_{CO_2}$ are more accurate at the higher values.

## Interpretation of Ventilation-$P_{CO_2}$ Response Curves

*Definition of Respiratory Effects.* It is easiest to discuss change in the ventilation-$P_{CO_2}$ response curves in terms of parallel displacement or change in slope.[15, 17, 18] However, other terms have been used. Some workers have described a change in threshold (intercept). This implies extrapolation of the response curve to the point where zero ventilation would occur. The $P_{CO_2}$ at this point is the threshold. This appears to us to be a potentially dangerous and misleading operation. First, one must have a linear response curve, in order to carry out the extrapolation in any reasonable manner. Second, if extrapolation is carried out on the basis of the experimental data without insisting that all extrapolated lines be parallel, then a slight change in slope can cause a great change in threshold which may not be a valid estimate of drug effect. Third, all extrapolation procedures tend to introduce additional variability into the data which leads to a loss of precision. In theory, threshold changes should only be used in cases of parallel displacement.

The term sensitivity should be reserved for a change in slope. However, the use of the term sensitivity may cause confusion. If the ventilation-$P_{CO_2}$ response curve is displaced to the left of normal, then at any given $P_{CO_2}$ a higher ventilatory response is produced than in the normal and in terms of the general meaning of the word sensitivity one would be justified in saying that the respiratory center was more sensitive to $P_{CO_2}$. Some have tried to avoid this by saying that the latter case was one of increased responsiveness—reserving sensitivity for changes in slope. However, it would appear best to use the terms slope and displacement where possible since there can be little confusion between them.

*Carbon Dioxide Excretion versus Alveolar $P_{CO_2}$.* If the data in figure 1 are plotted with $CO_2$ excretion perpendicular to the alveolar ventilation-alveolar $P_{CO_2}$ plane, then a 3 dimensional surface is obtained. The different $CO_2$ excretion isopleths (fig. 1) represent sections of this surface parallel to the alveolar ventilation-$P_{CO_2}$ plane. This surface can also be viewed from the $CO_2$ excretion-alveolar $P_{CO_2}$ plan in which case a curve as shown in figure 4 is obtained with its ventilation isopleths. In figure 4 respiratory depression is represented by the area to the right of the normal response curve.[17] In general, this is not a particularly useful or informative plot. A parallel displacement of the ventilation-$P_{CO_2}$ response curve becomes a nonparallel displacement with this type of plot. In terms of the control of respiration by the respiratory center

a plot of ventilation versus $P_{CO_2}$ seems to be more pertinent.

*Ventilation Changes with Parallel Displacement.* Parallel displacement of the response curve produces a more marked effect on ventilation at elevated concentrations of inhaled $CO_2$ than when the subject is breathing room air.[19] This can be readily understood by examining figure 5. Net $CO_2$ excretion must remain constant at equilibrium, and hence the ventilation must lie along the $CO_2$ isopleth. At the same time ventilation must lie along the response curve. The actual ventilation is determined by the intersection of the $CO_2$ isopleth and the response curve. As shown in figure 5, the ventilation effect with displacement of the response curves is greater at elevated levels of $P_{CO_2}$, *b*, than it is with room air, *a*. Because of the "hockey stick" (see previous section, fig. 3) effect in after drug response curves, the effect *a* on room air is even less than that shown in figure 5.

*Relationship Between Changes in Response Curve and Effects Upon Respiratory Center.* There has been some reluctance to attribute drug-induced changes in the ventilation-$P_{CO_2}$ response curve as due to the effects of a drug upon the respiratory center. There are indeed many things which may affect the response curve without having an effect on the respiratory center (table 1).[23, 24] When the type of

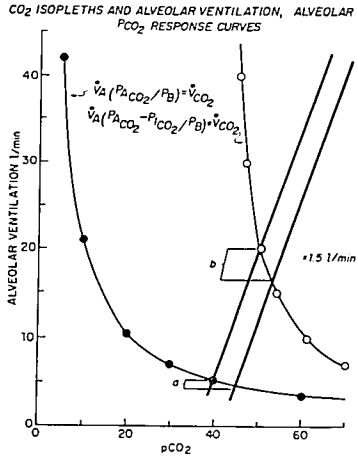


FIG. 5. Respiratory response curve (before and after drug) and $CO_2$ isopleths representing a constant net $CO_2$ excretion for a subject breathing room air and 5.3 per cent $CO_2$. *a* and *b* represent observed changes in alveolar ventilation due to drug induced displacement of the response curve. The magnitude of the drug induced changes of alveolar ventilation varies markedly with the concentration of inhaled $CO_2$. The effect of the drug induced changes on the response curve is more constant. (By permission New York Academy science).[19]

TABLE 1

MECHANICAL FACTORS THAT EFFECT CARBON DIOXIDE RESPONSE CURVE

| Factor | Effect on Response Curve | Reference |
|---|---|---|
| 50 ml. decrease in dead space | Parallel displacement to left 0.5 mm.Hg $P_{CO_2}$ | 15 |
| 25 per cent decrease in cerebral blood flow | Parallel displacement 3.3 mm. to left | 15 |
| 10 per cent increase in cerebral blood flow | 0.7 mm. to right | 23 |
| 50 per cent decrease in lung compliance | 50 per cent decrease in slope (assuming no feedback) | 15, 20 |
| 100 per cent increase in airway resistance (laminar flow) | Less than 1 per cent change in slope | 15, 20, 21 |
| Pulmonary A-V Shunt (10 per cent) | Parallel displacement to left 1.1 mm.Hg $P_{CO_2}$ | 15 |
| One liter decrease in functional residual capacity | Parallel displacement to left 0.2 mm.Hg $P_{CO_2}$ | 23 |
| 25 per cent decrease in cardiac output | Less than 0.1 mm.Hg $P_{CO_2}$ displacement to left | |

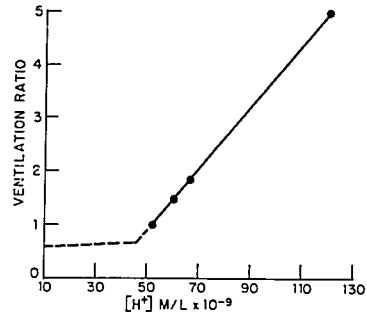


FIG. 6. Ventilation ratio as a function of hydrogen ion concentration. The solid line is taken from the work of Domizi, Perkins and Byrnes[25] on dogs. The dashed line is an approximation based on the data of Poppell, Yamamee, Roberts and Randall.[27] The dashed line is in disagreement with the work of Gray.[26] The shape of this combined curve offers a possible explanation for the increased respiratory depressant effect of morphine in the presence of alkalosis.

effect and its magnitude are considered it is clear that many drugs must have an effect directly on the respiratory center and the effect cannot be due to the extraneous factors listed in table 1. Substantial parallel displacement of the ventilation-$P_{CO_2}$ response curve is almost certainly due to an effect upon the respiratory center. A change in slope may or may not represent respiratory center effects.

*Additive Effects of [H+] and $P_{CO_2}$.* A combination of slope and displacement effects due to respiratory center effects is occasionally seen because both $P_{CO_2}$ and hydrogen ion concentration [H+] affect ventilation and the latter is a discontinuous linear function, *i.e.*, the curve breaks and changes slope at a concentration about normal (fig. 6). When the ventilation-$P_{CO_2}$ response curve is obtained by inhaling $CO_2$ two simultaneous changes occur: an increase in tissue $P_{CO_2}$ and hydrogen ion concentration. The response curve is the resultant of both effects and both effects stimulate respiration. For [H+] above normal ventilation increases linearly with [H+].[25] The same holds true for $P_{CO_2}$ concentration.[26] The two effects are additive and it must follow that the final response curve is linear and has a steeper slope than that for either $P_{CO_2}$ or [H+] effects separately (fig. 7). If a drug completely inhibits the effect of either $P_{CO_2}$ or [H+] on respiration, it must cause a change in slope of the ventilation-$P_{CO_2}$ response curve.

At H+ concentrations below normal the [H+] has no or little effect upon respiration. This is apparent from the work of Domizi *et al.* (fig. 6).[25] Obviously, with below normal [H+] negative ventilation cannot occur, and so the curve flattens. Experimental proof of this flattening is contained in the data of Poppell *et al.*[27] When their data are recalculated and replotted according to [H+] versus ventilation ratio the dashed line shown in figure 6 results. Figure 6 contains an explanation for the frequent observation that patients in respiratory or metabolic alkalosis are more sensitive to effects of narcotic drugs on respiration than are normal individuals.[15] The narcotics depress the ventilatory response to carbon dioxide. With this depression there is an increase in [H+] which stimulates respiration and tends to nullify the depressant effect on the $P_{CO_2}$ response. The patient in alkalosis lacks this compensatory [H+] effect until the

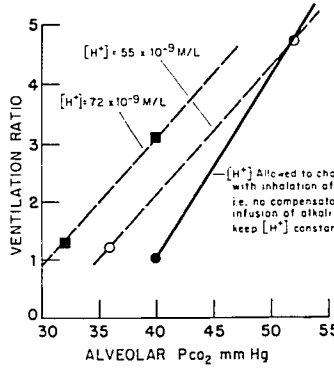


FIG. 7. Ventilation ratio as a function of alveolar $P_{CO_2}$. The data are taken from the work of Domizi, Perkins and Byrnes[25] on dogs and constitute a replot of their figure 3. The usual ventilation $P_{CO_2}$ response curve is shown as a solid line. The dashed lines indicate the response curves obtained when [H+] concentration is kept constant. Thus, the usual response curve is the sum of a $P_{CO_2}$ effect and a [H+] effect.

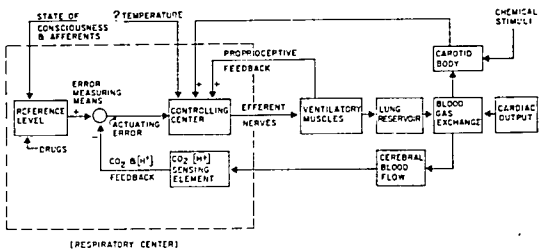


FIG. 8. Schematic representation of possible organization of respiratory center and some of the feedback loops involved in the control of respiration (see text).

$P_{CO_2}$ is elevated and $[H^+]$ rises. Thus, the alkalotic patient should show a flatter response curve than normal as has been found by Alexander and associates.[28] The response curve of the alkalotic subject should be markedly displaced by morphine, but at high levels of $P_{CO_2}$ the curve should show a steeper slope than the control curve. This complete sequence of events for morphine has not yet been experimentally verified.

The combined effects of $[H^+]$ and $P_{CO_2}$ might account for the fact that the slope of the response curve after morphine tends to be flatter than the control at low values of $P_{CO_2}$ and to rise parallel to the control curve only at higher values. If morphine produced some depression of the response of the respiratory center to $[H^+]$ (a parallel lateral displacement of the curve), then the subject receiving morphine might behave similarly to one who is mildly alkalotic.

From the foregoing it is clear on theoretical as well as practical grounds that is safest to discuss drug effects in terms of displacement of the response curve. Changes in slope can have a variety of interpretations. To achieve a parallel displacement it may be necessary to drive the $P_{CO_2}$ to relatively high values and this should be done where possible.

## Analysis of Respiration as a Servo Mechanism

If the $P_{CO_2}$ of the respiratory center increases ventilation is increased until the arterial and hence tissue $P_{CO_2}$ decreases. As pointed out by Grodins *et al.*[29] this chain of events constitutes a servo system in which $P_{CO_2}$ and $[H^+]$ are the main feedback signals. The difference between the feedback signal and some reference value generates the actuating error for control of respiration.

In figure 8 we have presented a mechanistic block diagram of the possible organization of a respiratory servo system. Although not anatomically accurate it is helpful in visualizing possible interrelationships.

In figure 8 it should be noted that brain tissue $P_{CO_2}$ concentrations should be calculated separately from body tissue $P_{CO_2}$ concentrations. It may even prove necessary to calculate respiratory center $P_{CO_2}$ concentrations as distinct from those of brain tissue.[9] A complete picture capable of accounting for drug effects would include $[H^+]$ and $P_{CO_2}$ effects as separate discontinuous linear functions (see preceding section). The slope of the $P_{CO_2}$ or $[H^+]$ versus ventilation response curve is apparently a hyperbolic function of tissue $P_{O_2}$ levels,[30] and thus hypoxia appears to influence the gain (sensitivity) of the respiratory center. Temperature elevation induced by being in a hot room apparently increases the slope of the ventilation $P_{CO_2}$ response curve[31] whereas temperature elevation induced by pyrogens apparently does not.[32] Temperature elevation due to being in a hot room may be primarily an effect on baroreceptors as suggested by Döring, Loescheke and Ochwadt.[22] The temperature effect shown in the servo control diagram is that of being in a hot room and should probably be shown as acting through baroreceptors.

In servo mechanism terminology the slope of the ventilation-$P_{CO_2}$ response curve represents the transfer function of the system. As such the slope is a function of the gain (sensitivity) of the respiratory center and of the efficacy of efferent nerve transmission, ventilatory muscle activity and proprioceptive feedback, lung function (compliance, airway resistance) and of gas exchange. Thus, any factor that influences any one of these variables will effect the slope of the response curve (transfer function) as pointed out previously (table 1).

Drugs that affect displacement of the alveolar ventilation-$P_{CO_2}$ response curve have their primary effect either on the reference level (threshold) of the respiratory center or by biasing the $CO_2$ and $[H^+]$ sensing element. If there is a slope change in addition to a displacement of the response curve the effect is more complex. Certain chemicals, such as sodium cyanide, will effect the slope of the response curve (transfer function) by acting through the carotid body reflex. This appears to represent positive feedback.

Sleep [33-36] as well as drowsiness [23] will affect the response curve. Since the primary effect of sleep is to cause a parallel displacement of the response curve it probably acts to reset the reference level (threshold) of the respiratory center.

## Respiratory Effects of Drugs

### Narcotics

*Morphine, Codeine and Synthetic Analgesics.* The respiratory response to $CO_2$ following narcotic analgesics has been investigated more extensively than that following any other class of drugs. There are many studies that illustrate the respiratory depressant effects of morphine.[1, 10, 11, 15, 36-38, 40-42] Studies of therapeutic doses of morphine indicate that its primary effect is to displace the response curve to the right with no significant change in slope.[11, 15, 37] Its primary effect at these doses appears to be, therefore, to change the threshold to $CO_2$ but not to change the sensitivity of the respiratory center. In a classic study, Loeschcke and associates, compared the respiratory effects of meperidine and morphine. They found that simple measurements of respiratory rate, depth or minute volume were inadequate indices of respiratory depression. However, by utilizing the respiratory response curves they calculated that 75 mg. of meperidine produced respiratory depression comparable to that seen following 10 mg. of morphine.[1] This is in agreement with the work of Prescott who reported 100 mg. to be more depressant than 10 mg. of morphine (86 mg. meperidine = 10 mg. morphine).[37] Morphine and meperidine have been used as standard drugs in a number of cross-over studies. Dihydrocodeine was shown to be a respiratory depressant [43, 44] and Keats and co-workers found that 60 mg. of dihydrocodeine produced respiratory depression equivalent to that seen after 10 mg. of morphine,[12] while in a cross-over study Seed *et al.* found 68 mg. to be equivalent to 10 mg. of morphine.[15] Morphine was compared to codeine by Lasagna and Beecher who studied the respiratory response to 5 per cent $CO_2$ and concluded that 120 mg. codeine produced as much respiratory depression as 10 mg. morphine.[41] In a recent analysis of respiratory response curves, 95.6 mg. of codeine was found equivalent to 10 mg. of morphine.[45] Similar results were obtained when the codeine was administered orally. Respiratory response curve effects of anileridine (Leritine) were compared to meperidine in another study by Keats *et al.* and 50 mg. was found to be equivalent to 100 mg. of meperidine.[46] Morphine, codeine, meperidine, dihydromorphinone, levorphan (Levo-Dromoran), alphaprodine and nalorphine were studied by Eckenhoff and associates [40] and all were shown to depress respiration. Methadone, *d,l*-isomethadone, *l*-isomethadone and dipipanone were studied by Prescott. Methadone 10.7 mg. produced respiratory depression equivalent to that seen with 10 mg. morphine.[37] In recent studies of response curve displacement .68 mg. of oxymorphone (Numorphan) [47] and 1.6 mg. of phenazocine (Prinadol) [48] were found to produce as much respiratory depression as 10 mg. of morphine. When all these reports are carefully analyzed and compared to the available data on analgesic potency there is no evidence to suggest that any commercially available potent narcotic produces significantly less respiratory depression than morphine when given in equi-analgesic doses.

*Narcotics plus Narcotic Antagonists.* Even more disappointing has been the work on the narcotic antagonists. Initially it was hoped and believed that the simultaneous administration of a narcotic and an antagonist, in an ideal ratio would yield a potent analgesic with little or no respiratory effects. In general the evidence indicates that when the narcotic and antagonist are given simultaneously, the respiratory depression is the same as that seen with the narcotic alone. Eckenhoff *et al.*[49] measured ventilation-$P_{CO_2}$ response curves and showed that levallorphan (Lorfan) alone depressed respiration and adding it to the narcotic, levorphan (Levodromoran), in ratios from 1 : 1 to 1 : 10 did not prevent respiratory depression. However, a cross-over study was not done. Bellville, Wallenstein, and Houde[50] did a double-blind, cross-over study using 4 subjects. They gave their drugs intramuscularly and assessed drug effects in terms of ventilation-$P_{CO_2}$ response curves. They found that levorphan 3 mg. plus levallorphan 0.3 mg. produced as much respiratory depression as the levorphan alone. In contrast to the foregoing Thomas and Tenney[52] did find a partial antagonism between levorphan and levallorphan when the two were given simultaneously. They used a cross-over study in 9 subjects and also assessed effects in terms of response curves. The major differences between their study and that of Bellville *et al.* appear to be: (1) Thomas and Tenney did not use the double-blind technique, (2) they used a proportionately larger amount of levallorphan (3.8 mg. of levorphan and 0.76 mg. of levallorphan), and (3) all drugs were given intravenously.

When nalorphine and morphine are given simultaneously, the respiratory depression seems to be as great as that after morphine alone. Lasagna and Beecher[54] did a double-blind, cross-over study in which respiratory effects were assessed in terms of changes in the respiratory minute volume following inhalation of 5 per cent carbon dioxide. They used subcutaneous injections of 2 mg. of nalorphine with 10 mg. of morphine and 5 mg. of nalorphine with 15 mg. of morphine. In both cases the combination produced as much respiratory depression as the morphine alone. Although they only measured respiratory minute volume in subjects breathing room air, Fraser, van Horn, and Isbell[51] found no difference between the simultaneous subcutaneous administration of 30 mg. of morphine combined with either 10, 6, or 3 mg. of nalorphine. In some doses or dose ratios the combination of narcotic and antagonist appears to produce little or no analgesia.[54] Thus, it appears that there is nothing to be gained from the simultaneous administration of a narcotic and an antagonist.

When either nalorphine or levallorphan are given one or more hours after the narcotic, clear-cut stimulation of respiration occurs.[11, 53, 55] At the same time the analgesic effects of narcotic also disappear.

*Narcotics plus Belladona Alkaloids.* It has been taught that atropine when given in combination with morphine would antagonize the respiratory depressant effects of morphine although a definitive study had never been made. Steinberg *et al.* carried out a double-blind factorial study and measured shifts in the respiratory response curve following atropine, morphine and the combination. They were unable to detect antagonism by atropine.[55] This is in agreement with the findings of Loewy[10] and parallels the results of Loeschcke and Wendel who studied response curves and found that 0.5 mg. scopolamine per 70 kg. body weight did not antagonize the respiratory effects of morphine.[58] It is well to remember, however, that doses of belladona that effect the body temperature may cause apparent respiratory stimulation.

*Narcotics plus Xanthines.* More striking has been the ability of xanthine derivatives to antagonize the respiratory depressant effects of the narcotics. In a study of the respiratory effects of intravenous aminophylline and meperidine (intramuscularly) alone and in combination in man, Stroud *et al.* were able to demonstrate a shift to the left of the response curve when aminophylline was given in a dose of 3 or 6 mg./kg.[56] The slope was increased significantly at the 3-mg./kg. dose. However, only three concentrations of $CO_2$ in oxygen were used to define this response curve. Julich has also shown that aminophylline displaces the curve to the left but he detected no change in slope.[57] When the response curve was determined after the administration of meperidine 150 mg. (intramuscularly) and aminophylline 6 mg./kg. (intravenously) the respiratory re-

sponse curve was not significantly different from the control.[56] In another study it has been shown that the simultaneous administration of caffeine (62.5 or 125 mg.) with either codeine (60 mg.) or morphine (10 mg.) antagonized the respiratory depressant effect of the narcotic.[58] The crucial question is: What effect does caffeine have on the analgesic potency?

### Tranquilizers

Of the phenothiazines, only the effects of promethazine and chlorpromazine on the respiratory response to $CO_2$ have been evaluated. Promethazine (50 mg.) was found to move the curve to the left (respiratory stimulation).[59] Chlorpromazine, 50 mg. intramuscularly, was found to diminish the respiratory response to 5 per cent $CO_2$.[60] This important class of compounds deserves more extensive study particularly in reference to possible interaction with the barbiturates and narcotic analgesics.

### Salicylates

The salicylates are respiratory stimulants. Alexander *et al.* reported an increase in slope as well as a shift in the response curve to the left following 1.8 to 2.4 Gm. of acetylsalicylic acid.[61] In the study of Samet and associates 1.8 Gm. of acetylsalicylic acid given three times daily produced a parallel displacement of the response curve to the left, but after one week the response curve had returned to normal. When acetylsalicylic acid was given again daily for one week along with acetazolamide (Diamox) 500 mg. the response curve was again shifted to the left but not as much as in the acute experiment.[62] Tenney and Miller administered 8 Gm. of acetylsalicylic acid daily for two days and noted in addition to the displacement of the response curve to the left, an increase in slope.[63] When they administered sodium salicylate (2 Gm.) intravenously a parallel displacement of the response curve to the left was observed. The difference in slope effects observed may be related to the dose of salicylate studied.

### Hormones

Since the observation that pregnancy and the luteal phase of the menstrual cycle are accompanied by a compensated hyperventilation (normal *p*H, low $P_{CO_2}$),[22] there has been interest in the respiratory effects of progesterone. During pregnancy the response curve is shifted 8 mm. of mercury $P_{CO_2}$ to the left and there is no change in *p*H.[64] Heerhaber *et al.*[65] found that a dose of 50 mg. progesterone in the adult male would move the curve 4 mm. of mercury $P_{CO_2}$ to the left. Döring *et al.*[22] found a shift to the left of 2.18 mm. $P_{CO_2}$ following 50 mg. progesterone and a shift of 1.42 mm. $P_{CO_2}$ to the left following 25 mg. estradiol. When both drugs were given simultaneously there was a shift of 3.30 mm. of mercury $P_{CO_2}$ to the left. In a recent study Lyons and Antonio[66] found a shift to the left (3 mm. of mercury $P_{CO_2}$) and an increase in slope following 50 mg. progesterone daily. There was no change in *p*H or electrolytes. Testosterone has no effect on the response curve.[65] Desoxycorticosterone acetate has been reported to cause an increase in $P_{CO_2}$[65] but its effects on the response curve haven't been measured.

Other hormones will also cause a shift in the $P_{CO_2}$ response curve. We recently observed a patient with severe myxedema and followed the parallel shift of the response curve to the left over a two month period during treatment with triiodothyronine (Cytomel).[67]

### Anesthetic Agents

*Intravenous Agents.* A truly definitive study of the effect of anesthetics on respiration has not been reported. However, there is evidence to suggest that the anesthetics, like the narcotic analgesics, do depress responsiveness of the respiratory center, the degree of depression varying directly with the depth of anesthesia. There is ample work to show that the barbiturates depress respiration. Beecher *et al.* showed that the response to 12 per cent $CO_2$ varied with depth of anesthesia with hexobarbital (Evipal) and thiopental (Pentothal)[68] and that the stimulatory effect of anoxia is still present when there is no response to 12 per cent $CO_2$.[69] This is in agreement with the data of von Euler and Soderberg who measured vagal efferents from the respiratory center in animals which were mechanically ventilated. He found that chloralose would decrease the response to carbon dioxide but did not affect anoxic reflexes.[70, 71] Kao and Belford[72] measured the response to various concentrations of

inhaled $CO_2$ and found a parallel displacement of the response curve to the right in light levels of anesthesia; at deeper levels they found a decrease in slope. In very deep anesthesia there was no change in ventilation up to 120 mm. of mercury. They also observed a shift of the respiratory response curve to the left after nalorphine during thiopental anesthesia.[72] It is difficult to evaluate the meaning of this observation, but it is likely that spontaneous lightening of anesthesia accounts for the results. The interaction of opiate premedication with thiopental was studied by Helrich *et al.* In electroencephalographic levels 1 and 2 there was minimal but definite respiratory depression as evaluated by the response to rebreathing endogenous $CO_2$ and the effects of the opiates appeared additive to those of thiopental.[73] The same workers found respiratory effects of barbiturate premedication were insignificant which is in agreement with the work of Keats and Kurosu[74] who reported respiratory depression following 200 mg. pentobarbital but stimulation following 100 mg. Patrick *et al.* studied the respiratory response to 5 per cent $CO_2$ during thiopental anesthesia and found a direct relationship between the electroencephalographic level and the ventilatory response.[75] They stated that the major effect of thiopental was to displace the response curve with a minimal change in slope. This was borne out by some preliminary observations of Compamanes and Bellville,[76] who studied respiratory response curves during various electroencephalographic levels of thiopental-oxygen anesthesia. The displacement of the response curve to the right varied directly with the depth of anesthesia (fig. 9), and in level 4 no change in ventilation was noted up to an alveolar $P_{CO_2}$ of 70 mm. of mercury. Hydroxydione (Viadril) produced results comparable to thiopental. There was a similar degree of respiratory depression at comparable electroencephalographic levels.

*Inhalation Agents.* The respiratory response to carbon dioxide during ether anesthesia has been studied only superficially. There is no doubt that the actions of this and other volatile anesthetics are complex.[77] Pulmonary reflexes affecting respiration are stimulated.[78] Acid-base balance changes occur, conduction at the myoneural junction may be impaired, and

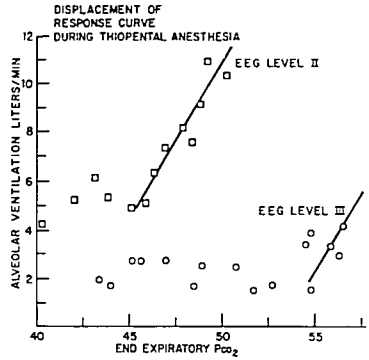


FIG. 9. Respiratory response curves obtained at electroencephalographic levels 2 and 3 during thiopental-oxygen anesthesia.

catecholamine release may occur. Studies, therefore, have been inconclusive often because of inadequate control or lack of sufficient data. Gordh reported that during deep ether anesthesia 12 per cent $CO_2$ would still stimulate respiration but the response was depressed.[79] Certainly the respiratory center of man is still sensitive to $CO_2$ at electroencephalographic levels 3, 4 and 5.[80] The response to $CO_2$ is decreased as anesthesia deepens.[26] Theoretically one would expect a shift to the left and an increase in slope (due to reflex stimulation) of the response curve during light ether anesthesia and as ether anesthesia is deepened a progressive shift to the right (due to depression of the respiratory center) and decrease in slope (due to block at the myoneural junction).

Cyclopropane depresses the response to $CO_2$,[50] but no information is available on its effect on the respiratory response curve slope. Nitrous oxide apparently causes a shift in the response curve to the left.[81] Halothane has been shown to depress the response to 5 per cent $CO_2$ and this response varies inversely with depth.[82]

## Muscle Relaxants

Muscle relaxants would not be expected to exert a direct effect on the respiratory center. Theoretically they should cause a decrease in

slope of the response curve. We have observed this to occur in one subject who received 15 mg. edrophonium (Tensilon) while on the respiratory response curve computer. There was a decrease in slope that persisted until the myoneural block (as manifested by diplopia) was dissipated.

### Catecholamines

A definitive study of the respiratory effects of norepinephrine in man has been done by Cunningham *et al.*[85] They infused 8–15 μg./minute of norepinephrine at a $P_{O_2}$ of 140 mm. of mercury and noted an increase in the respiratory response curve slope but no change in intercept (displacement). They discuss the role of norepinephrine in relation to hypoxia and express the belief that the respiratory effects of hypoxia are not due to the release of norepinephrine.

### Summary

From the foregoing it is obvious that while many studies of respiratory effects of drugs have been done, information on this subject is still meager. Most studies purporting to show absence of respiratory effects are valueless since respiratory depression was not accurately defined or measured or the sensitivity of the method employed was not demonstrated. The inability to detect a characteristic does not mean it does not exist since at higher dose levels or with a more sensitive method it may be found.

Even when considerable care is exercised in the design and execution of experiments, identical results are not obtained even when two groups of investigators employ the same methods. Reports by Keats and co-workers consistently show a mean displacement of the response curve one hour after morphine that is almost twice the mean one hour displacement that our group at Memorial Center reports. Examination of the protocol does not reveal the answer to this difference, but in discussion it has been brought out that the subjects in the studies by Keats and co-workers were selected from among those medical students who showed the largest responses to morphine. In our own studies no selection of subjects on the basis of response to morphine has been made. The selection of subjects enables one to achieve greater statistical precision in a relative potency assay but carries with it the hazard that generalizations to the population at large may not be as valid as with a nonselected group, *i.e.*, those giving a marked response to morphine may give no response at all to some other drug which is a depressant in some subjects. Selection of subjects on the basis of their response to morphine carries with it the implicit assumption that whatever drug is being studied is merely a stronger or more dilute form of morphine. This assumption is of course necessary in any relative potency assay, but there may be times when it does not hold, and selection of subjects may lead one to overlook such exceptions.

A cross-over experimental design in which each subject serves as his own control leads to a more precise comparison of drugs. As this technique becomes more widely used, it is hoped that the quantitative data so obtained, particularly that on drug interactions, may lead to a better and more precise interpretation of the mechanism of drug action.

Many compounds used by the anesthesiologist deserves more extensive study. There appears to be an urgent need for controlled respiratory studies on such agents as muscle relaxants, tranquilizers, and analeptics. Moreover, studies already completed but with the use of healthy volunteers need to be extended to patients with disease, particularly those with electrolyte imbalance and those with respiratory disease. Such studies might well help to elucidate the cause of the occasional "untoward" reaction.

At present it seems most advantageous to express respiratory effects of drugs in terms of their effect on response curve displacement and slope. Undoubtedly techniques will be evolved so that the transfer function of each component in the feedback loops that control respiration can be analyzed and differential equations derived to express this servo system and the effects of drugs on it. Only then will the effects of drugs on the respiratory response to carbon dioxide be completely understood.

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