THE INTERPRETATION OF RESPIRATORY
DRUG EFFECTS IN MAN

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The evaluation of a drug effect on the respiratory mechanisms depends not only on what the experimenter chooses as a measure of response, but on what interpretation he places on it. Few bother to define either respiratory stimulation or respiratory depression, and it is often apparent that many observations reported to show either would, in effect, be less convincing if a sound definition were adhered to.

For normal man breathing ambient air at sea level, respiratory homeostasis may be defined in terms of alveolar ventilation (alveolar ventilation = expired volume — dead space ventilation). For any given metabolic carbon dioxide output the tension of CO₂ in the alveolar air (or arterial blood) varies inversely as the alveolar ventilation and represents the most ready index of change in effective ventilation. Since it is clear that evaluation of either a stimulatory or depressant effect rests on knowledge of the change in effective alveolar ventilation, it is difficult to draw conclusions from data which indicate only the change in minute volume or respiratory frequency under a drug. Occasionally, what appears to be a stimulatory effect is quite the opposite, because if the frequency has increased proportionately more than the expired volume, only the dead space is more thoroughly ventilated.

It is less commonly appreciated that many drugs studied for their influence on the respiratory system also have significant effects on the body metabolism and may change oxygen consumption and carbon dioxide output. If the respiratory control mechanisms are functioning adequately, alveolar ventilation will be set at a new level to maintain the carbon dioxide tension at the normal value. If this new level is in exact accord with the change in metabolism, the CO₂ tension will be unchanged and, by definition, there has been neither stimulation nor depression of respiration since the respiratory economy of the body is unaltered. This, in spite of the fact that the observer will record external measurements which may indicate profound changes in minute volume and respiratory frequency, and by calculation, alveolar ventilation. But the alveolar and arterial CO₂ tensions will remain unchanged. Only change in alveolar ventilation beyond that predicted

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from the change in metabolism can be ascribed to a direct drug effect on the respiratory mechanisms.

To facilitate understanding these inter-relationships, the following diagram has been devised (fig. 1). In it, the alveolar CO₂ tension is indicated on the abscissa and the level of metabolic CO₂ production on the ordinate. The latter is expressed in relative units so that control value is always 1. If CO₂ production falls to half during an experiment, this would be indicated at the 0.5 value. Oxygen consumption is indicated also as a relative value, but this scale is valid only if the respiratory exchange ratio is the same during the control and experimental periods. Absolute values of CO₂ output and oxygen consumption can readily replace the relative values indicated, but the convenience of comparing heterogeneous populations becomes more complicated. As the relative scales are indicated, if the absolute amount of CO₂ produced per unit time were 800 cc. during the control period, this would replace the 1.0 on that axis; if the respiratory exchange ratio were 0.8, the value 1,000 cc. oxygen consumed during the same period would replace 1.0 on the oxygen consumption scale. The indicated multiples of these absolute amounts would simply replace the dimensionless relative values indicated.

Because the alveolar ventilation is directly proportional to the CO₂ produced and inversely proportional to the alveolar CO₂ tension, we
may plot relative alveolar ventilation isopleths. These are seen as a family of straight lines radiating from the origin. They become progressively nearer a vertical position as the alveolar ventilation ratio becomes indefinitely large, since only at infinite alveolar ventilation is the alveolar CO₂ tension zero. The normal alveolar point, marked A, lies at the point of intersection of the alveolar ventilation line labeled 1 and the relative CO₂ production level 1. For normal man at sea level, this normal alveolar point would project vertically down to indicate an alveolar CO₂ tension equal to 40 mm. Hg.

Movement of the alveolar point following the exhibition of a drug can be rigidly interpreted if two of the three variables, alveolar CO₂ tension, alveolar ventilation, and CO₂ production, are known from the experiment. By definition, any movement of the point to the right (shaded semicircle) is associated with a rise in alveolar CO₂ tension and may be said to represent a depressant effect of the substance on the respiratory mechanism. If no metabolic factor is implicated, the point will move horizontally along the line marked 1°, indicating a primary drug effect. All effects in the shaded area below the alveolar ventilation line, 1, will be associated with a decrease in measured alveolar ventilation. Note though that in the right upper octant (above alveolar ventilation line 1), the experiment would record a rise in measured alveolar ventilation, but this would still represent a net respiratory depressant drug effect because the alveolar ventilation failed to keep pace with the metabolic increase in the carbon dioxide output which the drug had caused. Purely vertical displacements of the alveolar point along the pathways labelled 2° are respiratory effects which are entirely secondary to changes in metabolism. Any movement of the alveolar point in the semicircle to the left is associated with a fall in alveolar CO₂ tension and if this has been produced by a drug, it may be said to be a respiratory stimulant.

Particular attention is called to the fact that movement into the left lower octant (open area below alveolar ventilation line 1) is respiratory stimulation even though the experimenter would record a fall in alveolar ventilation. There are scattered data which indicate that many drugs which have either stimulant or depressant effects on respiration also have significant effects on metabolism (1–4). In some instances these metabolic effects may be so impressive that it is easy to formulate erroneous conclusions about primary respiratory effect without quantitative knowledge of the metabolic factor (5). It is probably relatively rare for a drug effect to be “pure” in the sense that under its influence the alveolar point will move in an entirely vertical or horizontal position from the norm.

For convenience, the simultaneous changes effected in the arterial blood, as the alveolar point changes, are indicated at the top of the diagram. The curved line is a portion of the CO₂ dissociation curve, assuming a normal blood bicarbonate level of 25 millimols per liter.
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Iso pH lines calculated from the Henderson-Hasselbalch equation are indicated and labelled. The arterial point is found by projecting vertically from the alveolar point until the CO₂ dissociation curve is met; the pH is then read directly. Movement of the alveolar point to the right is associated with underventilation (respiratory depression), and a concomitant shift of the arterial point into the shaded area is indicative of acidosis. Similarly, movement of the arterial point into the range of uncompensated respiratory alkalosis follows respiratory stimulation (and a fall of arterial CO₂ tension). This curve cannot be applied to chronic drug effects in which a renal response has been stimulated to alter the plasma bicarbonate and thus determine a new CO₂ dissociation curve nor, for the same reason, is it directly applicable if the added agent is of sufficiently acid or basic character to titrate the blood directly.

Another major problem in evaluating a respiratory drug effect is to define some stimulus which may be appreciated and quantitated with the measured respiratory response. For the ideal experiment this should be a single stimulus, all others being held constant. Such an ideal is rarely met, but practical compromises may be designed. Since it is probably true that most respiratory drugs act predominantly via the central nervous system, CO₂ is the stimulus of choice although the hydrogen ion effect will always be involved. Either the inspired (6) or alveolar (arterial) CO₂ tension (7) may be utilized, though the latter is of greater advantage since when this value is plotted against the resultant response (measured as alveolar ventilation) a nearly linear relationship results.

Figure 2 illustrates such plots for a normal subject and the way they may be altered by drugs. Two features are of interest: Since the slope of these lines indicates the amount of change in alveolar ventilation for each increment in alveolar carbon dioxide tension, it may be regarded as a measure of the "sensitivity" of response of the respiratory center to CO₂ (and hydrogen ion). Further, extrapolation of the ventilation line to the CO₂ axis (alveolar ventilation equal zero) provides a concept of "threshold" (8) since this is the largest CO₂ tension for which there is no ventilatory response. This concept must not be taken too literally and attempts to establish this value experimentally always provide a value slightly higher than predicted.

It is important that many drugs acting on the respiratory center appear to affect these two modalities somewhat independently. Although the entire clear area represents respiratory stimulation, this may occur without demonstrable increase in "sensitivity," for example, ammonium chloride effect (8), or with marked increase in "sensitivity" as seen at high altitude (9), or after the prolonged administration of salicylates (5). The shaded area, on the other hand, indicates respiratory depression which may be accompanied by marked decrease in "sensitivity," as seen with morphine and other narcotics.
(10), or which may occur without change in "sensitivity," apparently the effect of some compounds reported to antagonize chemically related depressants (11). The cause for these different effects is not clear, but it has been tempting to speculate that in many instances (but not all) changes in "sensitivity" parallel changes in the buffering capacity of the blood (12), but this explanation is inadequate to explain acute effects.

With few exceptions, respiratory drug effects on peripheral chemoreceptor mechanisms have been largely neglected. Breath holding studies may be designed to illustrate changes in oxygen threshold, but they are difficult to perform and may be dangerous. In general, such peripheral actions are best exhibited in the experimental animal.

Drugs which affect the circulatory system may secondarily produce alterations in respiration. This will be particularly true if the pulmonary circuit is altered. It is not known whether it is possible by drug action to open latent pulmonary arteriovenous shunts or to disturb the normal ventilation-perfusion relationships of the alveoli. If these actions were possible and the resultant effect were to cause many alveoli to be effectively underperfused, the remainder would have to be overventilated in order to make up for the areas which would be unable to eliminate carbon dioxide. The effect would be equivalent to adding to the dead space.

**Summary**

Respiratory stimulation or depression has been defined in terms of the economy of the carbon dioxide tension existing in the blood and
alveolar air. Drug effects have been considered from this respect and the way they may influence respiratory measurements has been discussed.

REFERENCES