DRUGS AND RESPIRATION[1]

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In spite of the many uncertainties which presently limit the understanding of respiratory physiology and pharmacology, the respiratory control system lends itself to quantitative pharmacological study perhaps better than does any other basic neurophysiologic regulatory mechanism. The reasons for this are several and include: (*a*) the manner in which the integrated output of the neuronal groups that drive respiration can be quantitatively and accurately measured in functional terms (e.g., as pulmonary ventilation or as work of breathing); (*b*) the ability to modify and drive the activity of the respiratory control system to greater functional output by natural chemical agents such as CO_2; (*c*) the existence of identifiable afferent nervous influences upon respiration (chemoreflexes, stretch reflexes) which have made it possible in drug studies either to eliminate selectively such factors in the overall respiratory control system, or purposely to exaggerate their influence; and (*d*) the discrete, phasic nature of respiration, which enables pharmacological investigation to be made of individual cells or small cell groups identifiable as parts of the respiratory neuronal complex. These abilities, to identify, to separate, to specifically stimulate, and to quantitate, are investigative assets which deserve full exploitation both in physiology and pharmacology.

Available information, current concepts, and research trends relating to respiratory regulation are described in several publications (43, 66, 91, 94, 103–105, 183, 205, 215, 244, 283, 343, 348, 353, 403, 404, 411). While these reviews do not present a unified interpretation of respiratory control, they do offer the findings which have resulted from the recent resurgence of interest in this topic and indicate the numerous questions which lend themselves to study by pharmacological means.

From existing information it is clear that the overall system of respiratory control consists of interlocking components which include mechanical, neurogenic, and chemical factors and also involves the counterbalancing of central and peripheral influences (215). The fundamental chemical mechanism of excitation of central respiratory neurons and cells of the chemoreflex sensing organs is not known, hence the mechanisms whereby certain excitatory or inhibitory drugs act upon these neurons remain uncertain. However, it is known that, at rest, a rhythmic central drive is modified both centrally and reflexly by the chemical products of metabolism and by the level of oxygen tension in the arterial blood; this chemical control of resting ventilation is modified by neurogenic influences originating in the lungs and associated with the mechanical act of respiration itself. In

[1] The detailed survey of literature pertaining to this review was concluded in July 1964. Selected later references were subsequently added.

exercise, prominent neurogenic influences arising in the periphery appear to provide the gross respiratory control with chemical regulation superimposed to act as a fine adjustment increasing or suppressing respiration in accordance with the level of metabolic activity (103, 215). The composite of respiratory stimuli, whether the chemical influences so important at rest or the interacting neurogenic and chemical influences in exercise, is capable of producing a respiratory response 20 times greater than the normal level of activity at rest. This is the range of activity available for alteration by drugs and for study of drug actions.

Respiration can be influenced by drug actions which alter not only the neuronal reaction to a particular stimulus, but also modify the degree of stimulation, the transmission of respiratory nerve impulses, the systemic, central nervous and pulmonary circulations, and even the properties of the lungs and airways. While drugs can influence respiration only by modifying existing functions, the overt effects of any drug may differ in either nature or degree in various physiological or pathological states. Because of the great variety of possible effects, it is necessary to establish a scope for this review which will have practical limits while emphasizing the breadth of work and opportunity in respiratory pharmacology.

The many sites of drug actions which affect respiration are summarized in Table I, together with illustrative references. Emphasis will here be given to pharmacological influences upon the regulation of respiration rath-

TABLE I

SITES OF EFFECT OF DRUGS MODIFYING INTERPLAY OF RESPIRATORY CONTROL AND PULMONARY FUNCTION

Locus of action	Example	Reference
Respiratory chemocenters	H^+	404
Reticular activating system	CO_2	205
Sleep "center"	Barbiturates	407
Vagal centers	CO_2	97
Cerebral cortex	Morphine	399
Spinal nerve roots, phrenic and intercostal motoneurons	Procaine	330
Skeletal neuromyal junctions	Neostigmine	206
Vagal ganglia	Hexamethonium	48
Bronchioles	Epinephrine	48
Pulmonary glands	Methacholine	55
Pulmonary vessels	Aminophylline	19
Carotid and aortic chemoreceptors	Nicotine	183
Pulmonary and coronary receptors	Veratridine	21
Brain circulation	Aminophylline	361
Myocardium	Digitalis	137
Renal tubules	Acetazolamide	47

er than to effects upon pulmonary function. This review will leave to others such important aspects of respiratory pharmacology as the effects of drugs upon pulmonary circulation (19, 418), the influences upon pulmonary secretions (54-57), the therapy of asthma and emphysema, the alteration of pulmonary edema (55, 384), cough (60), the blockage of respiratory impulses by spinal anesthetics, and the pharmacological improvement of respiration in myaesthenia gravis (206).

Techniques for Studying Respiratory Effects of Drugs

Choice of animal.—While the relative importance of various control components may be quantitatively dissimilar in various animals, many species in addition to man are required in the study of respiratory pharmacology. However, the system of respiratory control, as with other multicomponent and highly sensitive neural mechanisms, is grossly and unevenly depressed in reactivity even by small doses of the anesthetic drugs required for the dissection involved in studies of higher pathways and localization of drug effects (122, 123, 265). Hence, both the existence and the magnitude of important physiological and pharmacological phenomena have often been obscured by narcosis of the very mechanisms being studied. The use of narcotized animals introduces still other problems related to the considerable influence upon respiratory reactivity of small changes in temperature, acidosis, and hypoxia. Such influences make control of the internal milieu an essential condition in studies of respiration under anesthesia.

The handicap of the stable resting state.—Another difficulty inherent in respiratory pharmacology relates to the handicaps imposed upon the investigator conducting studies in the resting, air breathing state, even in the absence of the complications concerned with general anesthesia. As already mentioned, respiratory regulation at rest is accomplished by a large number of interdependent chemical, physical, and neural feedback systems so interlocked that a disturbance in one component of the system promptly results in alterations of others (103, 215, 254, 370). In the comfortable respiratory state of eupnea, psychological and other influences, such as the degree of wakefulness, can upset the balance of physiological controls and introduce new bases for a respiratory change (40, 141, 142, 205, 314).

Compensatory changes.—When an imposed condition or an administered drug alters alveolar ventilation out of proportion to effects upon metabolism, a change in the pressures of alveolar gases (P_{CO_2}, P_{O_2}) must result (43, 214, 215, 254, 370). These changes are reflected almost immediately and nearly completely in the arterial blood and in the cells of the peripheral chemoreceptors, and later in the fluids and cells of the central nervous system (215). Thus the effect of a drug upon respiration leads also to changes in the local environments of the chemoreceptor and central respiratory neurons and hence affects the stimulus level at these locations. This change in stimulus level usually limits the degree of the overt drug effect. For example, a drug-induced respiratory depression leads both to a rise in arterial

P_{CO_2} and to a decrease in P_{O_2}; these together increase the degree of bombardment of the depressed respiratory mechanisms, and thus limit the extent of ventilatory depression. To determine the true magnitude of a respiratory depressant effect upon neural structures, it is necessary to compare control and post-drug measurements at the same physiological stimulus levels (92, 228, 254).

The stable-state CO_2-ventilation response curve.—Limitations of the resting state in unanesthetized human beings have led to the procedure of conducting quantitative studies of respiratory drug actions while intentionally imposing a chemical respiratory drive or other stress as part of the experimental conditions. This is done not only to minimize the psychic influences which can have such prominent effects in the unstressed state, but also to exaggerate the magnitude of the stimulant or depressant drug action being studied (228, 254). The stressing procedure now most generally used is administration of CO_2 at various inspired tensions (42, 131, 228, 254, 307, 370); the ventilatory response to these increased CO_2 tensions provides a CO_2-ventilation response curve (219).

The CO_2-ventilation response curve is itself an expression of a drug action on respiration, the drug in this case being CO_2, which produces the most powerful respiratory effect of any known agent. Once obtained, the CO_2-response curve is a highly useful baseline for studying the actions of other drugs on respiration and respiratory control. The normal, predrug response to CO_2 indicates the overall respiratory reactivity to a physiologically important stimulus. It is valuable as an index of respiratory reactivity even though the mechanism of action of the CO_2-related stimulus is not yet known.

Drugs can affect the reactivity to CO_2 in a variety of ways. The CO_2-response curve may be modified by action of a drug not only upon central neurons but also upon any of the components of the respiratory system, from the glomus cells of the carotid body, through the phrenic neuromyal junction, and even to the smooth muscle cell of the bronchiole. The advantages of employing CO_2-response curves include both the ability to make comparisons of drug effects at similar stimulus levels and the gross magnification of drug effects which results from measuring their effects upon a "driven" system. An important disadvantage of this method is that considerable time is required to obtain the succession of measurements from which the CO_2-response curves are constructed. Methods of continuous recording and plotting have been devised to facilitate initial data processing in essentially stable-state studies (41). However, during the lengthy period of exposure to the various tensions of CO_2 required for construction of CO_2-response curves, changes may occur in the absorption, distribution, excretion, and metabolism of the drug being studied. This limits the usefulness of the stable-state CO_2-response method to drugs known from other studies to have a long duration of action. It is also important to recognize that the slope and the position of a normal CO_2-ventilation response curve

are not the same for all normal individuals (214) and may vary considerably from one measuring period to the next even in the same subject unless precautions are taken to avoid fatigue, excitement, bladder distention, and other extraneous factors.

The respiratory response of animals and men to administration of gases containing increased concentrations of carbon dioxide was originally evaluated only in relation to the inspired concentration of CO_2 (122, 174, 256, 265, 288, 307). It is now considered inaccurate to employ inspired P_{CO_2} or the percentage of CO_2 as the stimulus index since the level of arterial P_{CO_2} will depend upon the ventilatory response produced as well as on the P_{CO_2} inspired. Failure to recognize this will lead to gross underestimation of the effect of a stimulant or depressant drug (254). Awareness of the inadvisability of employing inspired P_{CO_2} as a stimulus index has led to the present use of alveolar P_{CO_2}, arterial blood P_{CO_2}, or even internal jugular venous blood P_{CO_2} as indexes of the chemical respiratory stimulus (117, 226, 232, 254, 289). Quantitative comparisons of one drug with another at the same stimulus level may now be made graphically at any particular elevated alveolar P_{CO_2} using CO_2-ventilation response curves (219, 254). It is of course also possible to compare the magnitude of alveolar P_{CO_2} associated with a particular level of pulmonary ventilation before a drug is given with the P_{CO_2} associated with the same level of pulmonary ventilation following drug administration (353). The methods involved in these two approaches are the same, whether one chooses to express a drug action as change in output of the affected system or as change in stimulus required to produce a particular output.

Potential usefulness of P_{O_2} alteration in stable-state CO_2-response studies.—(a) Decreased arterial P_{O_2}.—Appraisal of drug effects upon the stable-state respiratory response to CO_2 at low alveolar oxygen tension (P_{O_2}) is an important addition to the methods available for quantitative drug evaluation in man (92, 93, 289). It offers the possibility of separating drug effects upon a respiratory system driven by actions of increased P_{CO_2} from the effects of the same drug upon the respiratory response to subnormal alveolar oxygen tension. Hypoxia apparently magnifies the chemoreflex component of respiratory control. It should be pointed out that since changes in P_{CO_2} increase chemoreflex activity as well as causing the more direct central stimulation of respiration, the situation is too complex to consider that use of the hypoxic state will permit clear separation of a drug action on a peripheral chemoreflex pathway from an action mediated through central chemosensitive neurons or other central components of the control system. Nevertheless, the employment of CO_2-response curves in normal and hypoxic states should provide an additional basis for thought and for study in respiratory pharmacology. In extending this method it is also important to recognize the existence of other effects of hypoxia, not only in relation to the reactivity of central neurons, but also with respect to increase in brain circulation (204) and the consequent lowering of the central nervous sys-

tem P_{CO_2}. The latter can be considerable, leading to diminution of the central P_{CO_2} stimulus level at the same time that the chemoreflex stimulus is exaggerated by hypoxia (215).

(b) Increased arterial P_{O_2}.—In constructing CO_2-response curves using mixtures of CO_2 in 21 per cent O_2, the induced hyperpnea results in an increased alveolar P_{O_2}. In view of the manner in which small elevations of P_{O_2} alter the ventilatory response to CO_2 (247), it may eventually become advisable to perform P_{CO_2}-response studies with a fixed alveolar P_{O_2} (e.g., at the level associated with air breathing at rest) (219, 225).

Administration of oxygen at partial pressures above one atmosphere may offer still another opportunity for a separate study of drug actions upon the central and chemoreflex components of respiratory control (219). The respiratory response to CO_2, diminished only about 12 per cent by oxygen administration at sea level (104, 118, 225, 247), is decreased to about 50 per cent of normal at oxygen pressures between two and three atmospheres (108, 218, 225). The cause of this respiratory depressant effect of very high P_{O_2} is not yet known. In view of indications that high partial pressures of oxygen reduce the reaction of the peripheral chemoreceptors to hypercapnia and acidemia (139, 188), the possibility has been raised that exposure to very high oxygen pressures may provide a readily reversible means of chemically denervating the peripheral chemoreceptors and isolating the central respiratory mechanisms in man from the influence of peripheral chemoreflex stimulation by either lowered oxygen tension or increased P_{CO_2} (225). As with the converse approach of driving the centers by the reflex effects of hypoxia (93), this method requires considerable further study to evaluate its importance in respiratory pharmacology (219).

Exercise as a baseline condition for drug studies.—It is very likely that advantages will result from performing drug studies under conditions other than the resting state. Although there is considerable uncertainty regarding the importance of various physiological factors in the production of exercise hyperpnea (91, 103, 215), the respiratory stress in exercise may provide an opportunity to appraise drug effects upon neurogenic components of the system of respiratory control (219). On this basis the study of respiratory effects even of familiar drugs may lead to increased understanding of both the drug actions and the underlying mechanisms of respiratory regulation.

Studies during changing states of drug action.—As in drug studies using stable-state CO_2-ventilation response curves, transient effects of drugs upon respiration can be masked or minimized by secondary changes in alveolar gases. When it is desired to learn the rate at which respiration is altered by or recovers from the effects of an administered drug, methods can be used for imposing and maintaining fixed levels of alveolar gases (92, 228). For moderate rates of change, periodic measurement may be adequate, but when the drug action is fleeting, breath-by-breath monitoring and control will be necessary (223). With such methods it is possible to

demonstrate the action of drugs which are rapidly inactivated after intravenous administration.

Choice of respiratory measurement.—During stable-state studies in the normal animal or man, the overall output of the respiratory mechanisms is quantitatively well expressed by the respiratory minute volume (V_E), or liters of gas moved per minute. This value, representing total pulmonary ventilation, includes both alveolar ventilation and the ventilation of the physiological dead space. Alveolar ventilation alone is not an appropriate index of the total respiratory drive, since the volume of dead space per breath is altered both by depth of breathing and by carbon dioxide administration (215), and the per minute ventilation of dead space is affected by changes in respiratory frequency.

While in the past it has been customary to report drug effects upon respiratory minute volume, it is now advisable to measure respiratory frequency and depth as well. As understanding of respiratory control improves, these individual expressions of respiratory activity may provide more specific bases for appraisal of drug actions upon respiratory neurons than does respiratory minute volume. The latter, as the product of frequency and tidal volume, is more a mathematical entity than a universal index of neuronal activity. In individuals with defective pulmonary or thoracic structure [e.g., emphysema (151), obesity (74, 151), or skeletal abnormalities], the movement of gas by the lungs may be so inefficient that "work of breathing" rather than respiratory minute volume should be used to provide a reliable measure of integrated ventilatory drive (22, 151, 273, 320, 322).

Respiratory Effects of Physiological Gases

The gaseous agents to be considered here will be limited to the natural respiratory gases, oxygen, carbon dioxide, and nitrogen, and to other gases employed in physiological situations (such as helium in diving). The effects of pulmonary irritants, of hemoglobin inactivation, and of enzyme poisons such as carbon monoxide (243) or hydrogen cyanide and the great variety of organic inhalants will not be considered except to call attention to the existence of important respiratory consequences of such forms of intoxication.

Oxygen.—The influences of oxygen lack (hypoxia) are considered in the section concerned with drug effects upon chemoreflex mechanisms. In addition to relieving gross or small degrees of hypoxia, oxygen in excess of normal concentrations or partial pressures produces several distinct respiratory effects. These additional effects, described in detail elsewhere (32, 104, 215, 218, 221, 310), include:

(*a*) Development of pulmonary oxygen toxicity when oxygen at tensions higher than normal is breathed for extended periods of time. At one atmosphere of inspired P_{O_2}, toxic irritation is detectable in 15 to 24 hours (85) and becomes extreme in one to three days (34, 111). At two atmospheres severe pulmonary toxicity develops within ten hours. The limit of

P_{O_2} for continuous administration has not yet been established, but it appears to be greater than 200 mm Hg in exposures of over one month (390).

(*b*) The development of pulmonary atelectasis. Inhalation of pure oxygen, by displacing nitrogen, causes the alveoli to be occupied only by freely absorbable gas. Atelectasis then may be promoted under certain conditions of obstruction (310), chemical irritation (302), or acceleration (408). This effect is of considerable interest in space medicine (125, 216, 344).

(*c*) The occurrence of an abrupt decrease in ventilation (26, 104, 118, 218) and a decrease in the slope of the respiratory response to administered CO_2 (225, 247). Each of these effects, which occur when oxygen is administered to normal individuals, has usually been considered to be due to relief of a residual "hypoxic respiratory drive." However, since elevation of inspired oxygen tension to one, two, and three atmospheres progressively increases the respiratory depressant action of oxygen, it is likely that oxygen produces depression by some other means which is not dependent upon relief of a presumed "residual arterial hypoxemia" (108, 118, 221).

(*d*) The occurrence of a slight but sustained hyperventilation during oxygen breathing by normal, unanesthetized individuals after the initial, abrupt fall in ventilation (32, 104, 226, 250). This respiratory stimulation appears to be an indirect effect of oxygen breathing. It is most probably related to the central accumulation of CO_2 which occurs when the oxygen needs of the medullary neurons are supplied by O_2 in physical solution; hemoglobin, circulating unchanged, then does not play its normal role in the transport of CO_2 (32, 157, 218, 226). This form of indirect respiratory stimulation by oxygen appears to coexist with the previously mentioned depression by oxygen of the ventilatory response to CO_2, such that the overall consequence of oxygen inhalation is a composite of the two opposite effects (218, 221, 225).

(*e*) The production of severe respiratory depression or apnea. Marshall & Rosenfeld demonstrated that, in the presence of respiratory depression produced by narcotic drugs, oxygen administration leads to further depression of ventilation, even to the point of apnea (265). This exaggerated effect of oxygen, related to abolition of the hypoxemic chemoreflex activity which sustains respiration in severe narcosis (183, 265), is also observed in transient form when oxygen is administered to normal individuals (106, 118, 250).

Patients with the chronic ventilatory insufficiency of pulmonary emphysema show respiratory depression on oxygen administration (81, 84, 184, 355, 393), sometimes associated with a deepening mental confusion or even development of unconsciousness (84). It is considered that at least part of this effect is not related to a diminution of hypoxic chemoreceptor activation, since the effect of oxygen is not always abrupt (184). The degree of oxygen depression of breathing appears to be least when the pre-existing acidemia is most severe (300). Since acidemia should contribute to respiratory drive not only centrally but by way of the peripheral chemoreceptors,

and is immediately exaggerated by any oxygen-induced respiratory depression, the respiratory influences of oxygen in chronic pulmonary insufficiency must be considered to include more than a decrease in chemoreflex bombardment of the central nervous system.

Carbon dioxide.—It is interesting and important that CO_2, which is structurally one of the simplest of drugs, produces the most powerful respiratory stimulation. It causes stimulation of central sites not yet clearly defined, by mechanisms as yet unknown, and it has peripheral chemoreflex actions whose quantitative relation to the overall stimulation is still uncertain (94, 165, 215, 217). While it is convenient to use change in P_{CO_2} as an index of the CO_2-related respiratory stimulus, it is necessary to point out that molecular CO_2 itself has not yet been shown to stimulate any nervous structure (217). Carbon dioxide passes freely through cell and tissue membranes (191), and due to its hydration, a change in the concentration of molecular CO_2 is necessarily accompanied by changes in hydrogen ion activity. The latter may be more directly responsible for the respiratory stimulant effects of CO_2 (215, 403), in which case the proton can be considered the simplest of neuronal stimulant drugs. Thus, changes in either the P_{CO_2} or $[H^+]$ of the blood, or of fluids perfusing the ventricles of the brain, lead to respiratory stimulation (241, 252, 416, 417). Similarly, increases in P_{CO_2} and $[H^+]$ cause activation of the carotid chemoreceptors in the cat (29, 139, 188), and it has been claimed that the influence of CO_2 is mediated by changes in $[H^+]$ for these chemosensitive structures also (189).

The rate at which respiratory stimulation develops following sudden administration of CO_2 does not correlate well with the induced changes of P_{CO_2} in arterial blood, brain venous blood, or cerebrospinal fluid alone (224, 232). While the time constant of P_{CO_2} change in arterial blood should resemble that in the peripheral chemoreceptors, it appears likely that central neuronal chemosensitive sites are influenced by CO_2 at rates quite different from those at which P_{CO_2} changes are produced in circulating blood and in cerebrospinal fluid (222). Certainly the central effects of CO_2 are modified by the chemoreflex stimulation simultaneously produced (321).

Carbon dioxide must be considered able to affect respiration by at least two mechanisms. One is the stimulation of breathing, effected at more than one peripheral and more than one central site (224). A second effect may be a depression of respiration by molecular CO_2 acting as an inert, narcotic gas. This depression may coincide with the stimulant effects of CO_2. The existence of a "narcotic" effect of CO_2 was postulated many years ago (238) and has been cited frequently. Usually emphasis is placed upon the possible transition from a stimulant to a depressant effect upon respiration (121). Actually, CO_2 administration to unnarcotized subjects appears capable of producing nearly maximal respiratory stimulation (215). However, in the absence of depressant drugs, the drastic consequences of breathing a very high concentration of CO_2 include the development of generalized

convulsions (271) which mask both the stimulant and the depressant effects of extreme hypercapnia (215). In the presence of emphysema (114) or of deep narcosis produced by drugs such as barbiturates with hypercapnia consequently related to inadequate pulmonary ventilation, the addition of CO_2 to the inspired gas may fail to stimulate breathing appreciably (or may even lead to further respiratory depression).

Inert gases.—The respiratory effects of inert gases such as helium, nitrogen, argon, neon, and krypton are difficult to study at sea level but can be elicited when the partial pressure is increased by use of ambient pressures greater than one atmosphere (72, 140, 149). Two different influences deserve mention, namely narcotic depression of the respiratory control mechanisms, and a mechanical interference with alveolar ventilation due to increased density of the inspired gas. No information exists concerning the relative degree to which inert gas narcosis affects central, as opposed to peripheral, mechanisms of respiratory control. The unearthly effects of very high inert gas pressures are described in relation to other aspects of the positive pressure environment in a recent symposium (179, 409). It is worth mentioning here that a narcotic effect of helium has not yet been demonstrated in man, even at partial pressures of 20 atmospheres. During vigorous voluntary hyperventilation, however, even helium is capable of limiting pulmonary ventilation (409). When interference with alveolar ventilation occurs at very high ambient pressures, especially during exercise, the resulting hypercapnia may further aggravate central depression (64, 233).

Drugs Affecting Stimulus Level

The activity of normally reactive respiratory mechanisms can be altered by change in the effective levels of respiratory stimulus to which chemosensitive components of the system are exposed. Thus, drugs which grossly alter the blood flow through the centers (340) or through the peripheral chemoreceptors (98, 230) should affect respiration. Oxygen administration affects respiration by producing a central accumulation of CO_2 (226). Changes in stimulus level mediated through drug actions which increase or, like morphine (280), decrease neuronal metabolism are most likely to be accompanied by changes in neuronal reactivity. Such effects have considerable bearing upon respiratory pharmacology.

Of the agents which appear to affect respiration by altering the acid-base stimulus level, three groups have received most attention. These are the acidifying and alkalinizing salts, the organic buffers, and the carbonic anhydrase inhibitors.

Acidifying and alkalinizing salts.—The injection or ingestion of acidifying salts, such as ammonium chloride or calcium chloride, produces effects upon respiration similar to those produced by infusing or ingesting hydrochloric acid, or infusing lactic acid (96, 113, 215, 403). In each instance, resting ventilation is slightly increased with a consequent fall in

arterial P_{CO_2}. The lowered arterial P_{CO_2}, which leads to similar decreases at many intravascular and extravascular sites, limits the degree of respiratory stimulation by the increased acid reaction of the blood. Largely because of this limiting effect it was commonly considered for several decades that the respiratory stimulation produced by metabolic acidemia was extremely weak and physiologically inconsequential. This is now known not to be the case since, as the arterial P_{CO_2} is restored to normal by adding CO_2 to the inspired air, the full and prominent respiratory effect of the metabolic acidosis becomes evident (96, 113, 215, 240). This respiratory stimulation by arterial acidemia, without hypercapnia, is then seen to be approximately one half that produced by CO_2-induced acidemia (215, 240). The influence of NH_4Cl upon carotid chemoreceptors has been studied (9, 195). It appears to cause a transient increase in electrical activity, but produces its major influence in respiratory stimulation via effects within the central nervous system (195).

Administration of alkalinizing salts such as sodium bicarbonate or sodium lactate produces a decrease in respiration which appears to have the same quantitative relationship to change in blood $[H^+]$ as does the respiratory stimulation by acidifying salts (215, 227). The possibility has been suggested that alkalinizing salts may decrease the reactivity to change in $[H^+]$ (199). However, when small doses are given, bicarbonate or lactate infusions appear to cause a parallel shift of the P_{CO_2}-ventilation response curve (352). In studies of the influence of altered blood acid-base reaction at experimentally fixed levels of P_{CO_2}, it has been possible in normal man to effect a quantitative separation of the respiratory influences of acidemia and hypercapnia (227, 240).

It has been repeatedly pointed out that when an acidifying or alkalinizing salt is administered either intravenously or by mouth to change the pH of circulating blood, the blood-brain and blood-cerebrospinal fluid barriers (109) prevent equivalent changes in pH from being produced in the cerebrospinal fluid and in the general brain tissue. Actually, since molecular CO_2 diffuses freely across the blood-brain barrier and cell membranes, the hypocapnia produced by the respiratory stimulation of metabolic acidosis leads to a decrease in the hydrogen ion concentration in the cerebrospinal fluid (323, 404) and, presumably, in the environment of some of the brain cells concerned with respiration. Cellular alkalosis should in these regions, therefore, coexist with intravascular acidosis (219). Thus, because the influences of a change in pH of the blood are accompanied by the central or peripheral effects of a change in the opposite direction in the pH of certain spaces in the brain protected by the blood-brain barrier, the overall respiratory effects of a drug-induced metabolic acidosis or alkalosis may appear small. There seem to be regions where no effective blood-brain barrier to charged particles exists, since administered sodium bicarbonate or HCl produces prompt respiratory changes (224). Such regions appear to be responsible for the full respiratory influence of metabolic acidosis (224).

Added in increasing concentrations to mock cerebrospinal fluid used to perfuse the fourth ventricle in the cat, ammonium chloride leads to transient increase in tidal volume followed eventually by respiratory arrest (251). It is evident that this represents a situation different from ingestion or intravenous administration of NH_4Cl (96), not only because of the previously mentioned influences of blood-brain barrier, but because systemically administered NH_3 is rapidly metabolized and should not achieve high concentration in central neurons.

Organic buffers.—Of the amine buffers, THAM, or tris(hydroxymethyl) aminomethane, has been the most extensively studied in relation to its effects on respiration (282). THAM is an amino-alcohol, a weak base, and therefore a hydrogen ion acceptor. In a solution, the reaction with acids such as carbonic acid is as follows:

$$(CH_2OH)_3C - NH_2 + HA \rightleftharpoons (CH_2OH)_3C - NH^+_3 + A^-$$

The effects of THAM during its infusion into normal men (59, 292) and into dogs (282) include decrease in arterial $[H^+]$, respiratory depression, and decreased CO_2 elimination, with little change in alveolar P_{CO_2}.

The respiratory depressant effect of infusing THAM intravenously is greater than that produced when a comparable lowering of blood acidity is produced by bicarbonate or lactate infusion (282). The greater influence is probably still related to alteration in $[H^+]$, but with the additional influence of decreased $[H^+]$ at extravascular and intracellular locations beyond the natural barriers to free movement of HCO^-_3. At pH 7.40 approximately 30 per cent of THAM is in the un-ionized state and thus may readily cross the blood-brain barrier to affect the environment of central neurons (261). Certainly this agent distributes itself in a fluid volume greater than the extracellular fluid space (242). Substitution of Tris buffer for the bicarbonate in solutions used to perfuse the cerebral ventricles leads to a progressive increase in pulmonary ventilation (381). This effect is surprising and unexplained.

It has been pointed out (257) that the respiratory depressant effect of the amine buffer, THAM, makes it unsafe as a means of correcting the acidosis of chronic pulmonary disease. It has been employed in the metabolic acidosis of diabetes (315, 337). This and similar agents should continue to have great importance as research tools.

Carbonic anhydrase inhibitors.—Intrinsically produced CO_2, presumably through the action of hydrogen ions formed in its hydration, is a prominent controlling factor in linking pulmonary ventilation to the requirements of body metabolism. The enzyme carbonic anhydrase accelerates the hydration of molecular CO_2 and the dehydration of H_2CO_3 according to the reactions

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO^-_3$$

These reactions proceed to the right in the metabolizing tissues and tissue

capillaries, and to the left for the CO_2 released from the blood in the pulmonary capillary. Since in each of these locations the blood is in the capillary little more than 1 sec (325, 326), studies of the kinetics of CO_2 hydration and carbonic anhydrase activity have had considerable theoretical and practical importance (263, 264, 325, 327, 328). Such studies have shown that the time constant (rate constant) for hydration of CO_2 is approximately 0.11 sec (328); for dehydration the time constant of 89.0 sec is much slower (45).

Roughton & Clark (328) have estimated that in the absence of carbonic anhydrase the hydration of CO_2 is slow relative to the time spent by the blood in the capillary bed. At body temperature the uncatalyzed hydration reaction is about 90 per cent complete only after about 200 sec (45). The absence of a detectable alveolar-arterial gradient for P_{CO_2} in normal man (215) indicates that the amount of carbonic anhydrase normally present and active in the red cells is sufficient to accomplish essentially complete dehydration of H_2CO_3 during transit through the pulmonary capillary (325). Analysis of red cells further indicates the presence of an amount of carbonic anhydrase sufficient to produce an approximately 5000-fold acceleration of the reaction between CO_2 and water (325, 327).

Inhibition of carbonic anhydrase by drugs such as sulfanilamide (329), or the more potent acetazolamide (45), and dichlorphenamide (284) can affect respiratory function in one or more of several ways, as follows:

(*a*) A decreased rate of hydration of CO_2 in the tissue capillaries may result in elevation of the P_{CO_2} and $[H^+]$ of the cells producing CO_2 as a result of their own metabolism (45). In the case of chemosensitive respiratory neurons, this should result in an increased stimulus level in the local environment.

(*b*) A diminished rate of dehydration of carbonic acid in the lungs appears to interfere with CO_2 elimination from the blood passing rapidly through the pulmonary capillary (45, 277). While the physical process of CO_2 tension equilibrium between pulmonary capillary and alveolus should proceed unhampered, a slow rate of dehydration leads to a situation in which the reaction proceeds to completion only after the blood has left the lungs. After leaving the alveolar capillary and without further exposure to a free gas phase, additional bicarbonate is converted to CO_2 with a consequent rise in arterial P_{CO_2} above the level which existed in the alveolar gas (45, 71, 276). This postulated intravascular increase in arterial P_{CO_2} results in a higher stimulus level at the peripheral chemoreceptors, in mixed venous blood (70), and at the central chemosensitive cells than would be expected from observations of changes in alveolar P_{CO_2} alone.

(*c*) Finally, by interfering with the important role of carbonic anhydrase in facilitating bicarbonate reabsorption in the renal tubule, the inhibitors of carbonic anhydrase allow the loss of sodium bicarbonate and accompanying water from the kidneys (368). This loss leads to a "metabolic acidosis" which provides a still further basis for respiratory stimulation.

The consequence of carbonic anhydrase inhibition in normal man is acidosis and CO_2 retention (240, 363), a prominent respiratory stimulation (68), and an alteration of the respiratory response to administered CO_2 (240). The CO_2-response curve is shifted to the left in a manner indistinguishable from the effect of acidifying salts such as ammonium chloride (240). The effect thus resembles the addition of a fixed acid stimulus rather than an alteration of neuronal reactivity (219).

Carbonic anhydrase inhibitors have been employed in the treatment of chronic respiratory insufficiency (77, 156, 284, 295, 303, 305, 332). The rationale of this therapy is that production of a metabolic acidosis will stimulate ventilation, lower arterial Pco_2, and improve arterial oxygenation. Any potential benefit thus must occur by way of renal actions of the drug, with benefit limited by pulmonary and central CO_2 retention (305) and by potassium depletion (77). When an improvement in ventilation is observed, it appears to be due to an increase in tidal volume leading to improvement in alveolar ventilation even though overall respiratory minute volume does not tend to increase (77, 284). Since circulating fixed acids may act upon different respiratory control mechanisms than those affected by the more freely diffusible CO_2 (224, 227), it is possible that the respiratory stimulation obtained by producing an acidemia may lead to a concurrent decrease in the central CO_2-related respiratory stimulus (215, 224).

Drugs and Chemoreflex Mechanisms

The central respiratory mechanisms are powerfully influenced by the electrical bombardment resulting from physiological chemoreflex activity, such as that generated by hypoxia (247, 289). They should therefore be driven by drugs which act upon the sensitive nerve endings of specialized peripheral chemoreceptors. Drug actions upon these physiologically important peripheral chemosensitive structures have been reviewed in detail by Heymans & Neil (183) and by Heymans (180). Additional summaries pertinent to these and other chemoreflex functions are contained in reviews by Comroe (420), by Dawes & Comroe (101), by Aviado & Schmidt (21), and by Dejours (104).

Actions of drugs on "nonphysiological" chemoreflex mechanisms.— Drugs may affect respiration not only by way of the anatomically demonstrated glomus cells of the carotid bodies and aortic arch (183), but also by actions upon other receptors in the heart, vessels, and lungs (21, 101). These pharmacological effects, designated as "pulmonary respiratory chemoreflex" (101), will be discussed in detail in the next review. They will here be described only generally for purposes of perspective.

The diffuse, pharmacologically activated, chemoreflex mechanisms apparently involve nerve endings not naturally sensitive to chemical constituents of the circulating blood. One such pharmacological reflex action appears to alter (by excitation or "sensitization," or by inactivation) the activity of the pulmonary receptors for the Hering-Breuer inflation reflex

(101). Still another action involves an effect on unidentified sensory vagal endings in the lung parenchyma. A partial list of agents which act by exciting these vagal sensory nerves appears in the review by Dawes & Comroe (101) and includes such diverse agents as nicotine, antihistaminics, veratrum alkaloids, adenosine triphosphate, ammonia, and 5-hydroxytryptamine.

Actions on carotid and aortic chemoreceptors.—The discrete structure of the carotid chemoreceptor, its prominent and measurable electrical activity, and its adaptability to isolated perfusion has aided study of the physiological and pharmacological factors involved in chemoreflex stimulation of respiration (83, 104, 144, 180, 183). The actions of pharmacological agents on chemoreceptors have been studied in their own right, and also have been employed as research tools in the so far unsuccessful attempts to elucidate the normal mechanisms of chemoreceptor excitation. From this great variety of excellent and purposeful studies has come information that chemoreflex activity can be qualitatively increased or blocked by several different types of agents (180, 183).

A serious limitation in the interpretation of studies so far performed has been the relative lack of quantitative information concerning (*a*) the degree of response of chemoreceptors to changes in the concentration of particular drugs and (*b*) the influence of the oxygen and acid-base environment of the chemoreceptors upon pharmacologic responses. The latter is important since in whole-animal experiments the beginning of respiratory stimulation both improves arterial oxygenation and causes a lowering of the arterial (and central) hydrogen ion concentration; each leads to a decrease in respiratory stimulus, and this secondary limitation of ventilation tends to obscure the full chemoreflex effects of pharmacological chemoreceptor stimulants. Methods for quantitation of electrical activity are now being applied to study of physiological activation of the carotid chemoreceptors (139, 189). As these methods became used for studies of drug actions, interpretation of chemoreceptor pharmacology should be considerably facilitated.

Table II summarizes studies of the agents and conditions capable of modifying impulse traffic over the nerve fibers from the carotid body. It should be noted that the nature and role of chemoreceptor activity has caused emphasis on study of drugs which stimulate, rather than depress, chemoreceptor discharge. Except for oxygen, carbon monoxide, and ganglion blocking agents (194), little information exists concerning agents having a depressant influence upon chemoreceptor activity. The respiratory effects of increased chemoreflex activity can be suppressed or obliterated by drugs acting at any one of many sites in the integrated respiratory system.

Physiological factors.—The chemoreceptors are stimulated by an increase in arterial P_{CO_2} or hydrogen ion concentration and are depressed in activity by a lowering of P_{CO_2} and $[H^+]$ (104, 139, 180, 189, 406). It is not yet

known whether these effects come from an intracellular or an extracellular action or both (189, 195). Presumably the effect of CO_2 is mediated in some manner via a change in $[H^+]$, rather than by an action of molecular CO_2. The actions of the latter should be depressant, as for any "inert gas" (266).

Fall in arterial P_{O_2} produces the well-known "stimulation of chemoreceptors by hypoxia" which interacts with the peripheral chemoreflex and central influences of carbon dioxide to produce the prominent hypoxemic hyperventilation. Since it is difficult to conceive that the lack of a substance,

TABLE II

EFFECTS OF DRUGS AND NATURAL SUBSTANCES UPON CHEMORECEPTOR ACTIVITY[a]

Agent or factor	Increases chemoreceptor activity	Decreases chemoreceptor activity	Representative references
Physiological factors			
↑ P_{CO_2}	*		53, 139
↓ P_{CO_2}		*	29, 139, 188
↑ P_{O_2}		*	49, 87, 139, 406
↓ P_{O_2}	*		139, 188, 406
↑ $[H^+]$	*		189, 193
NH_4OH		*	138
NH_4Cl	*		195
↑ Temperature	*		46
↓ Temperature		*	46
Drugs affecting carbohydrate metabolism			
Sodium cyanide	*		10
Sodium azide	*		350
Sodium sulfide	*		14
Sodium nitrite	*		350
Acetaldehyde	*		196
Methylene blue	*		350
2,4-Dinitrophenol	*		350
Adenosine triphosphate	*		13, 192
Sodium iodoacetate		*	13
Sodium malonate		*	13
Sodium fluoride		*	13
Sodium arsenite		*	13
Carbon monoxide		*	194

TABLE II *(continued)*

Agent or factor	Increases chemoreceptor activity	Decreases chemoreceptor activity	Representative references
Acetylcholine and related drugs			
Acetylcholine	*		396
Methacholine	*		405
Carbamylcholine	*		99
Physostigmine	*		17, 182
Diisopropyl fluorophosphate	*		382
Atropine	—	—	12
Ganglion stimulant and depressant drugs			
Nicotine	*		181, 414
Lobeline	*		181
Dimethyl phenylpiperazinium iodide	*		270
Hexamethonium		*	67, 115
Pentamethonium		*	115
Tetraethylammonium		*	115
Pendiomide		*	115
Trimethaphan camphorsulfonate		*	115
Tubocurarine		*	11
Other agents			
5-Hydroxytryptamine	*		270, 414
Veratrum alkaloids	*		20
Phenyldiguanide			414, 415

* See review refs. (83, 101, 104, 180, 183, 206, 353).

even of oxygen, can provide a positive basis for stimulation, the influence of lowered Po_2 is probably indirect. It is likely that, as oxygen pressure falls, there develops a progressive, qualitative change in metabolism (e.g., shift to anaerobic) which results in an exaggerated neuronal activity. It is of considerable importance to the understanding of chemoreceptor pharmacology to determine whether the effect of lowered Po_2 may in fact be related to or identical with the mechanism by which excitatory effects are produced by change in Pco_2 or $[H^+]$. The suppression of chemoreceptor activity by oxygen is apparently incomplete, even at a Po_2 of one atmosphere (139, 189, 406). It is possible that very high inspired oxygen pressures, up to three to five atmospheres, will be necessary to abolish entirely the natural chemoreceptor activity, and that increased oxygen pres-

sure may not only relieve any residual "hypoxic drive" (183) but may also exert an action involving suppression of the chemoreflex response to hypercapnia (218). Increased Po_2, at one atmosphere, does interfere with the respiratory response to cyanide injection in man and dogs (87, 122) but apparently not to lobeline (122). Perhaps surprisingly, increased Po_2 also inhibits the stimulation of chemoreceptors by acetaldehyde (196).

Temperature changes also affected the chemoreflex activity (46, 104, 183), but the basis for this effect is not clear. It is probable that the chemoreceptors do not possess unique temperature-sensing properties but that a change in temperature alters the hydrogen ion activity, the level of a metabolic constituent, or changes in another factor concerned with generation of action potentials. The effects of altered temperature upon the response of chemoreceptors to drugs have not yet received much, if any, attention.

Drugs affecting carbohydrate metabolism in chemoreceptors.—The metabolic rate of the carotid chemoreceptors is at least as high as that of brain tissue (98). Like the brain, these neural sense organs should depend predominantly upon glucose or other carbohydrate for energy metabolism. Hence drugs which, like cyanide, modify carbohydrate metabolism may be expected to cause gross changes in chemoreceptor activity. Examples of the effects of such drugs are reviewed by Heymans (180) and Heymans & Neil (183) and are summarized in Table II. Although the basis for chemoreceptor activation through effects on metabolism is far from clear, it is evident that most of the drugs listed can interfere in some way with the synthesis of high energy phosphates or with the integrity of the cytochrome oxidase system (14, 183). It will be interesting to learn the influence of oxygen toxicity upon the chemoreceptor and its response to drugs. Since the carotid chemoreceptor is a discrete structure whose blood supply can be isolated and whose functional output can be quantitatively measured in terms of electrical impulse frequency, it will provide a valuable opportunity for integrating electrophysiological, pharmacological, and biochemical methods in the search for a metabolic basis of neural activation.

Acetylcholine and anticholinesterases.—Acetylcholine stimulates the chemoreceptors, and its effects are exaggerated by anticholinesterase drugs such as physostigmine, and the organophosphorus compounds (180, 183). The latter appear to increase the response of the chemoreceptors to ACh without affecting the response to lobeline or cyanide (17, 180, 182). Atropine in ordinary systemic doses does not prevent chemoreceptor stimulation by acetylcholine (183), but has this effect when applied topically. Such observations have led to proposals that acetylcholine is the normal activator of the chemoreceptor (183, 245). Although acetylcholine may be found to play a role in impulse transmission within the carotid body, it is not at all definite that it is involved in the actual initiation of the activity. Recent studies on isolated chemoreceptors indicate that acetylcholine may be liberated during electrical stimulation of the carotid body (421).

Ganglion stimulant and depressant drugs.—The carotid chemoreceptors are also activated by agents such as nicotine, lobeline, and DMPP (dimethyl phenylpiperazinium iodide) which stimulate sympathetic or parasympathetic ganglia (180, 183). Hexamethonium and other agents which block autonomic ganglia tend to prevent activation by the ganglionic stimulants, even including acetylcholine (183). It further appears that the stimulant effects of low arterial Po_2 and cyanide can be elicited even after the block of the chemoreceptors produced by ganglioplegic drugs (62, 115). Such findings have raised questions regarding whether two distinct types of chemosensitive cells exist in the carotid body, whether they exist in series or in parallel, and whether a single chemosensitive cell may be activated by a variety of related but different mechanisms (183).

Other drugs affecting chemoreceptors.—The increased chemoreceptor activity produced by veratrum alkaloids is partly responsible for the tachypnea of the Bezold-Jahrish reflex (21, 183). Powerful stimulation is also produced by 5-hydroxytryptamine (serotonin) (270). The respiratory stimulant effects of vanillic acid diethylamide are both central and chemoreflex in origin (159), but are now known to be predominantly due to actions at a central site (61).

Central Depressants

Anesthetic agents.—The respiratory effects of general anesthetic agents in animals and man have been critically reviewed by Dripps & Severinghaus (123), who relate the findings to the concepts of interacting peripheral and central factors in respiratory control. Respiratory and pulmonary aspects of clinical anesthesia have also been reviewed by Allbritten (7). Other recent studies of individual agents relate to halothane (51, 107, 110, 142, 170, 234, 290, 383), cyclopropane (197), methoxyflurane (110), trifluoroethyl vinyl ether (383), and nitrous oxide (130).

All general anesthetic agents in use progressively depress the respiratory control mechanisms with increasing dosage, leading ultimately to death from central respiratory failure. All agents, as they produce respiratory depression, lead to respiratory acidosis and, unless administered with oxygen, to hypoxia. The combination of these derangements results in chemoreflex bombardment of the respiratory centers as well as to the circulatory consequences of increased sympathetic activity (309). If artificial respiration is employed, the gross chemical changes and their effects can be minimized.

The mechanism of the depressant effects of anesthetics upon respiration is probably almost entirely due to a narcotic action upon the complex neural network of respiratory control without significant interference with axonal or neuromuscular transmission, or contractility of respiratory muscles (123). Although diethyl ether and other agents do affect neuromuscular transmission (123), inspired ether concentrations up to 20 per cent do not produce a complete phrenic neuromuscular blockage (200); the respiratory

depression observed with ether at lower concentrations is therefore largely due to actions upon respiratory neurons.

Agents administered intravenously, such as thiopental and hexobarbital, produce depression of respiration without the irritant or other stimulant effects characteristic of certain inhalational anesthetics. They thus resemble other members of the family of barbituric acid derivatives (123, 279). An additional factor of practical importance is the occurrence of laryngospasm during light stages of anesthesia with the intravenous anesthetics (123).

In reporting a study of halothane in patients, Fink et al. (142) offered views on the manner in which anesthetics affect respiratory control. The concept states that the reticular activating system itself is CO_2-sensitive but nonrhythmical, and that the activity of the rhythmically firing respiratory neurons of the brain stem is increased by impulses from the CO_2-sensitive neuronal units of the reticular activating system. By producing a depression of the CO_2-sensitive cells of the reticular activating system, anesthetics may cause reduction in resting respiration and in the respiratory response to CO_2 (142).

It has been considered that as central components of respiratory regulation are depressed during anesthesia, the control of breathing shifts to the peripheral chemoreflex mechanisms (122, 123), which have been cited as more resistant to narcosis (123, 341, 342). In severe anesthetic depression there is no doubt that respiration can be sustained by chemoreflex activity after sensitivity to administered carbon dioxide has been lost (123). Although this is true, it should probably be considered that the entire complex of respiratory control mechanisms, including the chemoreceptors and the influence of chemoreflex impulses upon the centers, is progressively depressed as the dose of a narcotic is increased. The end point is failure of response to any stimulus (220). Just as chemoreflex influences can be depressed, the ability of expiratory and inspiratory vagal reflexes to affect respiratory centers can be diminished by narcotics such as urethane and barbiturates (345).

In severe narcosis, depression of the central respiratory control mechanisms should be exaggerated by extreme hypoxia. During oxygen administration, hypercapnia should add to a pre-existing degree of narcosis, and hypercapnia is capable of blocking the influence of chemoreflex stimulation in narcotized animals (178). For this reason the lowering of central P_{CO_2} from hypercapneic, possibly depressant, levels may allow central neurons to respond more fully to chemoreflex bombardment (18, 178). Conversely, administration of CO_2 enhances the narcotic effect of an anesthetic gas (269). Hence, further increase in the arterial P_{CO_2} of a severely narcotized, already hypercapneic patient or animal may so increase the depression of central neuronal structures that neither the central nor the chemoreflex stimulant effects of CO_2 will be expressed.

Stimulation of respiration is produced by certain volatile or gaseous in-

halational anesthetics. This is due to irritant, metabolic, or other effects which exist in addition to the depressant action responsible for the anesthetic property itself (51, 107, 172, 234, 342, 378, 383). The stimulant effects may tend to sustain respiration against failure, even in the face of progressively deepening central narcosis. In light anesthesia the stimulant property may cause respiration to be increased above normal. Examples of such stimulant agents are diethyl ether (200) and halothane (51). The respiratory stimulant changes produced by diethyl ether in light anesthesia include metabolic acidosis (123, 367, 374), increased sympathetic activity, release of catecholamines (123, 309), and a reflex tachypnea caused by its irritant action upon the lower respiratory tract (101).

The influence of the stimulant effects upon respiration changes with depth of anesthesia. In studies employing single fiber vagus nerve preparations, the effect of diethyl ether upon the rate of spontaneous discharge of both stretch and deflation afferents was found to depend upon the inspired ether pressure (395); the firing rate is increased by low and abolished by high ether tensions. Furthermore, low concentrations of inspired ether stimulate respiration in the decerebrate cat while at the same time diminishing the response to administered CO_2 (200). As the depth of anesthetic depression is increased, the diminished reactivity of central respiratory mechanisms is indicated by a decreased or even abolished respiratory response to administered CO_2 (200). The respiratory stimulation observed in light anesthesia is abolished by vagotomy (200). Although this has been considered evidence that diethyl ether causes "sensitization" of pulmonary receptors (200, 395), it is just as likely that the stimulation is due to the addition of a nonspecific chemical irritation rather than to a true sensitization of a mechanism normally activated by a physical force (stretch). Regardless of the basis for the increased vagal afferent activity, it is clear that, after vagotomy, increasing the concentration of inspired ether leads to progressive depression of respiration. After prolonged depression and in association with severe acidosis and anoxia, a secondary tachypnea may develop (200).

Narcotic analgesics.—As methods have improved for quantitative study of drug-induced respiratory depression in man, it has become possible to evaluate accurately the respiratory depressant properties of each new narcotic analgesic and to compare the new drug with a reference drug such as morphine. Methods employing magnification of ventilatory effects by CO_2-ventilation response curves or controlled iso-P_{CO_2} studies have been especially useful. The results of many such studies have been reviewed elsewhere (43, 135, 219, 379). Individual drugs which have been investigated include those listed in Table III.

Several observations of general pharmacological and therapeutic significance have come from these extensive quantitative individual studies and comparisons:

(*a*) Thus far it has not proven possible to devise an effective narcotic

TABLE III

CENTRAL DEPRESSANTS

Agent	References	Agent	References
Anesthetics		Narcotic analgesics	
Ether	51, 122, 123, 200	Morphine	33, 38, 120, 122, 124, 126, 129, 186, 231, 254, 255, 267, 287, 296, 297, 313, 349, 386, 392, 399
Chloroform	366		
Cyclopropane	122, 197, 308, 309		
Halothane	51, 107, 142, 234, 290, 308, 366, 383	Oxymorphone	38, 147
Methoxyflurane	110	Phenazocine	44, 164, 296
Trifluoroethyl vinyl ether	383	Meperidine	124, 129, 164, 190, 229, 236, 254, 287, 316, 364
Nitrous oxide	123, 130	Methadone	307
Ethylene	123	Anileridine	201, 365
Thiopental	130	Alphaprodine	419
Evipan	123	Propoxyphene	65
Narcotic antagonists		Dihydroxymorphinone	318
Nalorphine	33, 102, 129, 132, 231, 267, 392, 410	14-Hydroxydihydromorphinone	389
Levallorphan	33, 132, 147, 190, 287, 316, 366	Codeine	236, 311, 356
		Dihydrocodeine	134, 202, 349
		Levorphan	132

analgesic which does not at the same time produce respiratory depression in proportion to its analgesic potency (35, 43, 219). The universality of this relationship is discouraging in therapeutics. However, it may provide a useful indirect basis for investigating the common features of the mechanisms of drug actions upon the neurons concerned with respiratory control and relief of pain (35). Studies of narcotic effects upon transmission in pain pathways (399) may eventually prove to have bearing upon the suppression of respiration.

(*b*) The depression produced by narcotic analgesics most frequently takes the form of a decrease in the slope of the respiratory response to CO_2 (43, 219). This effect, prominently demonstrated for meperidine (254), is ordinarily considered as a decreased "sensitivity" to the CO_2-related stimulus. The possibility that a different effect can occur is indicated by the nearly parallel shift in the CO_2-ventilation response curve produced by moderate doses of morphine (219, 254). This latter form of respiratory depression by "parallel" displacement may involve an elevation in threshold to respiratory stimulation, a change in stimulus level (here an unlikely possibility), or inactivation of a component of the total control system. It is probable that higher doses of morphine will decrease the slope of the response to CO_2 as well as shifting the CO_2-response curve.

(*c*) Both the respiratory depressant effect and the duration of depression of a narcotic analgesic agent can be grossly increased by the effects of other agents (135) including anesthetics (130), barbiturates (130), and psychopharmacological agents (229). This means that a therapeutic dose of one drug which in itself may produce a clinically insignificant respiratory depression in a normal subject may lead to death from respiratory failure when its depressant action is imposed upon a system teetering on the borderline of competence (130, 229). This narcotic-induced exaggeration of respiratory insufficiency occurs not only when the primary depression is due to drugs, but also in respiratory inadequacy due to diseases such as pulmonary emphysema (124) and asthma.

Studies of the effect of morphine upon resting ventilation in aged patients did not reveal any evident difference in the degree of respiratory depression from that found in young men (186); however, since no CO_2 stress method was employed to prevent the damping effects of compensatory changes, a difference would probably not have been detected even it if had existed. The effects of aging on respiratory control and upon pulmonary mechanisms need additional study. Reasons for suspecting that susceptibility to respiratory depression by drugs should increase with age are presented to Eckenhoff & Oech (135).

Narcotic antagonists.—The degree of respiratory depression in severe morphine poisoning can be reduced by administration of the narcotic "antagonist," nalorphine (43, 135, 219, 410). This effect appears not to be predominantly due to a true antagonism of morphine actions by an opposing stimulation, since most of the actions of nalorphine are qualitatively the same as those of morphine itself (410). Each drug alone produces depressant effects such as drowsiness and analgesia, each has antitussive effects, and each causes respiratory depression. However, like morphine, nalorphine also has stimulant effects upon the central nervous system (410). These stimulant effects are prominent enough to produce convulsions in mice and monkeys (410). In decerebrate dogs nalorphine is found to produce a slight stimulation of respiration, leading some to the suggestion that the known respiratory depressant action is exerted chiefly on the higher centers (102).

In the initial phase of clinical evaluation of nalorphine in the treatment of overdosage with morphine, considerable confusion was generated by apparently conflicting evidence that nalorphine stimulated, that it depressed, or that it failed to affect the respiration of individuals depressed by morphine administration (135, 235, 410). Each of these observations was undoubtedly correct and at present it is generally considered that nalorphine, which is a respiratory depressant but of lower potency than morphine (43, 150, 219, 231, 372, 385, 392, 410), has a sufficiently high affinity for the same receptor sites occupied by morphine so that it successfully competes with morphine for these cellular locations (43, 135, 150, 219, 231, 372, 385, 392, 410). Studies in which morphine and nalorphine were administered to normal men, both separately and simultaneously, indicate that nalorphine has about half the respiratory depressant potency of morphine but about twice the affinity of morphine for the neuronal structures concerned with respiratory response to CO_2 (392). The result of this competitive inhibition is that the weak respiratory depressant effect of nalorphine is substituted for the more powerful respiratory depressant effect of morphine (135, 150, 235).

The early reports of a nalorphine-induced improvement in ventilation of animals (385) or individuals poisoned by a barbiturate (385, 410) kept alive the question of whether a stimulant effect of nalorphine contributes to its clinical usefulness as a narcotic antagonist. It now appears quite clear that in man, regardless of whether some of its central side effects are in fact stimulant in nature, nalorphine is a depressant drug and as such has no practical value in relieving the respiratory insufficiency produced by central depressants except the narcotic-analgesics (43, 135, 235, 410).

A consequence of using a weak respiratory depressant drug (nalorphine) to combat the effects of a more powerful depressant (morphine), especially when the antagonist has some stimulant actions, is that the overall effect will depend upon the relative doses of the narcotic and its antagonist. Thus, in severe morphine depression, administration of nalorphine should improve pulmonary ventilation. However, use of the same dose of nalorphine when the degree of depression by morphine is slight should cause exaggeration of respiratory depression due to the depressant action of nalorphine itself (135, 150, 410).

An additional concept of the basis for nalorphine action in relieving respiratory depression is that it may depend upon release of mechanisms responsible for physical dependence (235). Since this would also involve competition with morphine for receptor sites, the concept has much in common with the more widely held view.

In the clinical management of poisoning by narcotic analgesics, the narcotic antagonists are useful in adults, as well as in newborn infants depressed by narcotic analgesics absorbed through the placenta. The antagonistic effects against a number of narcotic agents have been studied and are summarized in a table by Woods (410) and in other reviews (135, 150,

235). The clinical employment, the dosage, and the side effects in such situations are also well described in several reviews concerned with narcotic analgesics or their antagonists (135, 150, 235, 410).

Hypnotics and sedatives.—Each of the organic sedative and hypnotic agents, from the barbiturate series through chloral hydrate and paraldehyde, is known on clinical grounds to produce respiratory depression. Respiratory failure is the cause of death in untreated individuals following overdosage; respiratory arrest can readily be produced by intravenous administration of such agents as thiopental. However, little quantitative information is available concerning the comparative potency and temporal characteristics of the respiratory effects produced by sedative and hypnotic drugs (Table III). Even when the magnification method for studying respiratory changes at elevated levels of alveolar P_{CO_2} is employed (219), hypnotic doses of barbiturates appear to produce less of a change in respiration (35) or even in the respiratory response to CO_2 than does sleep itself (40, 314). The slight respiratory depressant action of hypnotic doses of a drug such as seconbarbital may well indicate a locus or mechanism of central action on respiration different from that of the grossly depressant narcotic analgesics.

Central Stimulants

Probably most of the drugs which produce cerebral cortical excitation will also have central effects upon respiration. It has become customary to designate as "analeptics" or "restoratives" certain drugs which are especially effective in stimulating respiration (Table IV). This emphasis should not be considered as being based upon potency in terms of effect per unit dose but upon the relative absence of such other actions as cardiac or smooth muscle stimulation. Certain natural hormonal drugs such as epinephrine and norepinephrine are among the most potent of all the central respiratory stimulants (93, 394), but are not classed as analeptics.

Analeptic drugs.—The use of central nervous system stimulants to counteract excessive depression by barbiturates and other narcotics has largely been replaced by improved physiological supportive management of the respiratory and circulatory depression. The bases for this highly desirable trend are summarized in several discussions of analeptics and treatment of narcotic poisoning (2, 3, 78, 154, 167, 213, 313, 331) and include the following major considerations:

(*a*) When taken in large amounts, drugs such as the barbiturates may produce apnea lasting for one or more days and general respiratory, reflex, and circulatory depression lasting for many days. The short duration of the stimulant effect of most analeptic agents requires repeated administration and an impractical meticulous titration of the stimulant effect against the depressed state.

(*b*) The analeptic drugs, unlike the narcotic antagonist nalorphine, are powerful general central nervous system stimulants and are capable of pro-

TABLE IV

CENTRAL STIMULANT DRUGS

Agent	References	Agent	References
Dioxone	1, 260, 375	Vanillic acid diethylamide, ethamivan	8, 15, 61, 159, 212, 274, 333, 357,
Micorene, prethcamide	25, 30, 63, 86, 112, 171, 176, 203, 208, 258, 293, 373, 400	Doxapram	387
		Methylphenidate	79
Bemegride	128, 168, 169, 285, 319, 412, 413	Caffeine	39, 262, 339
Pentylenetetrazol	128, 412	Aminophylline	27, 33, 160, 347, 364
Dimefline	23, 31, 166, 338	Xanthine derivates	347
Amiphenazole, daptazole	127, 177, 246, 285	Sympathomimetic amines	28, 93, 145, 146, 168, 298, 309, 394
Lobaden	286		

ducing adverse effects such as convulsions even in the continued presence of high doses of a depressant drug.

(*c*) Use of a long-acting stimulant drug leads to the possibility of sustained toxicity and convulsions from excessive dosage.

(*d*) The survival of depressed patients treated by providing physiological support (artificial respiration and oxygenation, circulatory support, prevention of pulmonary infection) appears to be at least as good without the addition of central stimulants as when rational physiological treatment is supplemented by use of analeptic drugs (78, 136, 167).

For such reasons the analeptics will probably continue to have only limited usefulness in the therapy of drug-induced respiratory depression. However, drug therapy will again become important when an agent is developed which relieves the respiratory depression of barbiturate intoxication by a competitive mechanism, rather than by introducing the counter effect of stimulation. It is also possible that development of effective and long-acting chemoreflex stimulants will provide the desired respiratory drive without the complication of extreme cortical excitation.

Active search continues for central stimulants (198, 278) and interest is turning to drugs capable of providing a sustained increase in ventilation in individuals whose alveolar gas exchange is subnormal because of pathological states such as pulmonary emphysema in which there has been a possible acclimatization to the associated respiratory acidosis.

Table IV summarizes stimulant agents which have had clinical trial in chronic states of respiratory depression. In addition to the analeptic agents (167), drugs used have included xanthines, salicylates, and hormones (Table IV). Each has proven capable of reducing the degree of arterial hypercapnia, acidemia, and anoxemia of emphysematous patients, but the small margin between therapeutic effect and undesirable side reaction has prevented any one drug from emerging as highly practical in the therapy of chronic respiratory depression.

Sympathomimetic and other amines.—Both epinephrine and levarterenol increase resting respiration and the ventilatory response to elevated levels of alveolar P_{CO_2} (1, 4, 93, 146, 168, 394). The effects are masked by the development of hypocapnia (24) but are evident if alveolar P_{CO_2} is prevented from falling. It is probable that ephedrine, the amphetamines, and related sympathomimetic amines having central nervous system stimulant properties will also show respiratory stimulant effects when they are studied by methods capable of providing quantitative information.

Stable-state studies of rapidly metabolized agents such as levarterenol require administration of the drug by continuous infusion. When this was done and CO_2-ventilation response curves were constructed at different, subnormal levels of alveolar P_{O_2}, it appeared to Cunningham et al. that the respiratory stimulant effect of levarterenol was upon central components influenced by the afferent activity of the chemoreflex mechanism (93). How this effect is brought about is not certain, but the method employed in the attempt to separate reflex and central effects of drugs on respiration in man deserves extension. The stimulant effects of epinephrine, qualitatively resembling those of levarterenol, may be exaggerated by the additional factor of increased stimulus level, since the glycolytic effect of epinephrine leads to a slight metabolic acidosis (93, 394).

Infusion of 5-hydroxytryptamine intravenously also stimulates respiration in man by actions apparently not related to alteration of oxygen consumption (298). This amine has been shown in animals to stimulate respiration by actions on the carotid chemoreceptors (83, 183). Since in man the respiratory stimulation occurs within a minute, it has been proposed that the receptors involved are located on the arterial side of the circulation (298). 5-Hydroxytryptamine does not readily cross the blood-brain barrier (294), hence the central effects of this drug on respiration are not prominently expressed after intravenous administration. Following injection into the cisterna magna, respiration is stimulated but in association with gross depression of blood pressure and heart rate (209).

Xanthines.—Aminophylline has been shown to increase the respiratory stimulation produced by CO_2 in normal subjects (364); the effect is sufficient to counteract the respiratory depression produced by therapeutic doses of a narcotic analgesic such as meperidine (33, 364). Although a statistically significant increase in respiratory response to CO_2 was not found to occur with caffeine alone, stimulation undoubtedly occurs since in the same study

caffeine was shown to counteract respiratory depression by codeine and by morphine (39). It has been pointed out that, for relief of mild degrees of narcotic depression, stimulant agents such as the xanthines may be more useful than the competitive narcotic antagonists (219), since the latter are additively depressant when the degree of depression by the narcotic is small. As with the sympathomimetic amines, the circulatory actions of the xanthine derivatives limit their clinical usefulness. They have been studied in mitral stenosis (27, 160), in depression due to narcotic drugs, and in severe respiratory insufficiency secondary to pulmonary emphysema (27).

Salicylates.—Powerful and long-sustained respiratory stimulation by salicylates leads to the sequence of acid-base derangements, respiratory exhaustion, and death seen in children poisoned by aspirin or other salicylate compounds (76, 80, 249, 360, 401, 402). Respiratory stimulation occurs in animals following chemoreceptor denervation and vagotomy (360, 371). It develops slowly over many hours, even after intravenous administration, partly because of the limited rate and degree of passage of salicylate across the blood-brain barrier (100, 268).

Interpretation of studies utilizing stable-state CO_2-ventilation response curves is complicated by lack of adequate information concerning the time-course of the development and degradation of salicylate effects upon respiration. Without an awareness of when the effect of a given dose of salicylate reaches its peak, interpretation of stable-state CO_2-response studies is handicapped. Small doses of salicylate appear to cause only a shift to the left in the position of the CO_2-response curve, as would occur with an increase in central stimulus level (219, 335). However, larger doses lead both to the shift in position of the CO_2-response curve and to the increase in slope which denotes greater respiratory reactivity to CO_2 (5, 371).

The effects of acute administration of salicylate used for treatment of respiratory insufficiency (380) have been studied in patients with chronic pulmonary emphysema and hypercapnia (336, 388). In emphysema it leads to temporary lowering of arterial P_{CO_2} and decreased acidemia, as well as to a slight increase in arterial oxygenation (388). However, chronic salicylate administration provides improvement only in a few of these patients (388); it does not improve the impaired ventilatory response to administered CO_2 (336) or inhibit the exaggerated ventilatory depression produced by oxygen administration (336).

Whether salicylate produces its prominent central respiratory stimulation by a direct action on membranes or by causing a secondary metabolic derangement within the respiratory neurons is not yet clear. Interference with carbohydrate metabolism is produced by salicylate (301, 359). Direct injection of salicylate into the cisternal cerebrospinal fluid produces a prompt and gross respiratory stimulation; in a comprehensive study of salicylate-induced hyperpnea Tenney & Miller obtained evidence that both a direct central action and an increased rate of general metabolism are involved in salicylate hyperpnea (371).

Salicylate poisoning presents a challenging complex of problems to respiratory pharmacology and therapeutics. The prolonged primary hyperventilation leads to a gross lowering of arterial P_{CO_2} (5, 358, 371). The progressive metabolic acidosis which occurs as a result of renal adjustments and metabolic effects of salicylate can exaggerate the respiratory stimulation and hypocapnia (358). Nevertheless, since molecular CO_2 freely passes across cellular membranes and the blood-brain barrier, the arterial hypocapnia with or without arterial acidosis should tend to produce central neuronal alkalosis in regions protected by a blood-brain barrier, and an alkaline shift in the cerebrospinal fluid (215, 323, 404). Additionally, the arterial hypocapnia should severely reduce the flow of blood through brain tissue (237, 361). In the face of this composite of several forms of respiratory stimulation, attempts to correct the hypocapnia by administering CO_2 will lead to still more violent hyperpnea and respiratory distress. Furthermore, if intraneuronal acidosis resulting from metabolic derangements is a factor in producing the hyperpnea of salicylate poisoning, the therapeutic administration of sodium lactate or sodium bicarbonate (312) should diminish the respiratory drive only in part, even after entirely correcting the arterial acidemia. This is because bicarbonate immediately influences only about one half of the central region concerned with chemical respiratory control (222). Therefore, because of decrease in ventilation and rise in P_{CO_2}, the use of alkalinizing agents should lead initially to a further acidification of the cerebrospinal fluid and those portions of the brain tissue protected by a blood-brain barrier.

Agents Affecting Mood

Tranquilizing drugs, such as chlorpromazine and meprobamate, appear to decrease the respiratory reactivity to elevation of alveolar P_{CO_2} both in normal individuals (229, 317, 351) and in patients with chronic pulmonary emphysema (317). In normal men this effect seems to be related more to prevention of an excessive response to hypercapnia than to the development of a true depression (229). However, when chlorpromazine is administered concurrently with the narcotic analgesic meperidine, the resulting degree and duration of respiratory depression is grossly exaggerated over that which occurs with meperidine alone (229).

An abrupt respiratory arrest occurs when chlorpromazine is administered rapidly intravenously (346, 391) and may be followed by respiratory stimulation (346). Similar effects are produced by promethazine and diethazine (391). The respiratory inhibition is abolished by vagotomy (346, 391) as is most of the respiratory stimulation (346). These acute effects are considered to be related to actions upon pulmonary vascular receptors and, as such, will be considered in a subsequent review.

Central effects of chlorpromazine and other phenothiazines upon respiration have been studied in cats by administration into the intracranial ventricles (185). Chlorpromazine acts at a location related to the cerebral aqueduct to produce mild respiratory depression.

Scopolamine has been found to produce different effects upon the respiratory response to CO_2 in different subjects (255), increasing the reaction in some and decreasing it in others. The nature of the scopolamine effect persists during the depression of respiration produced by morphine (255).

The respiratory influences of "clinically" useful doses of the classical tranquilizer, ethanol, appear not to have been subjected to quantitative study, although respiratory depression and death in respiratory failure is the consequence of an overdose.

Although overall activity of the nervous system and activity of the respiratory system appear to be related (306), essentially no quantitative information exists concerning respiratory effects of the newer "psychic energizers" or even of the older amphetamine derivatives.

Central Cholinergic System

The potent anticholinesterases influence respiration by actions on structures outside the central nervous system such as the peripheral chemoreceptors (183), the neuromyal junctions of respiratory muscles, and the innervations of bronchial muscles and glands (206). Respiration is also prominently affected by actions of anticholinergic drugs upon central mechanisms of respiratory regulation. Studies of these effects, understandably performed upon animals other than man, are summarized in several reviews (158, 187, 275) and in a recent, comprehensive treatise on cholinesterases and anticholinesterase agents (206).

The physiological importance of acetylcholine and its esterases complicates quantitative study of the respiratory actions of cholinesterase inhibitors. Evidently the respiratory paralysis produced by organophosphorus compounds such as DFP (diisopropyl fluorophosphate) is produced by action on the central nervous system as well as at the neuromyal junction, since phrenic and intercostal electrical activity is decreased by this anticholinesterase agent (187, 210, 211).

Since cholinergic transmission at synaptic sites can be improved and then blocked by progressively slowing the rate of hydrolysis of acetylcholine, the effects of anticholinesterase agents upon respiration should vary not only with the agent but also with the dose at the site of action. Paulet has investigated in dogs the respiratory effects of DFP (diisopropyl fluorophosphate), TEPP (tetraethyl pyrophosphate), OMPA (octamethyl pyrophosphoramide), parathion, neostigmine, and physostigmine (299). In small doses each agent increased ventilation; in large doses all depressed breathing. The respiratory response to administered CO_2 was increased by the organophosphorus compounds but decreased by neostigmine and physostigmine. In the same study, atropine was found to partly reduce the effects of DFP, OMPA, and physostigmine, but not to affect the changes produced by TEPP, parathion, or neostigmine (187, 299). Since all anticholinesterases produce the same qualitative result, the failure of atropine to modify the effects of the latter group suggests that the anticholinesterases are not

similarly distributed within the central nervous system and that atropine may not readily reach certain sites of anticholinesterase action.

It is known that in intact animals the central respiratory effects of anticholinesterase drugs (299) or the effects upon the brain cholinesterase (187) do not correlate with the ability to influence anticholinesterase activity *in vitro*. Of considerable significance in respiratory studies are the observations that anticholinesterase drugs cross the blood-brain barrier at greatly different rates, depending in part upon the charge characteristics of the dissociated molecule (187, 207). It was found by Koelle & Steiner that intravenous injection of a tertiary amine anticholinesterase into rabbits readily inactivated 90 per cent of the total cholinesterase of brain, whereas the quaternary form of the agent did not measurably inhibit brain cholinesterase (207). Injection of the same drug into the lateral ventricle caused widespread inactivation of brain cholinesterase, indicating that an effective blood-brain barrier to the quaternary amine was responsible for its lack of influence when intravenously administered.

Other effects of anticholinesterase agents upon respiration are described by Krivoy et al. (210, 211), Wiemer (397, 398), and Aleksandrova (4). Their observations, indicating the existence of stimulant and depressant actions, must be considered in relation to the continuing uncertainty concerning the nature of the blood-brain barrier, and the possibility that the barrier is not uniform in the regions concerned with central respiratory control (222, 224).

Conceivably, a powerful anticholinesterase agent capable of free passage across the general blood-brain barrier will be an important aid in defining the relationships among neurohumoral and acid-base factors in central respiratory control and the sites of action of each. Since the central system of respiratory control has numerous components and probably many synapses, the centrally mediated effects of anticholinesterase drugs cannot be thought to occur only at a chemosensitive "respiratory center." The reticular activating system contains neurons somehow concerned with respiration (142), and this system is affected by acetylcholine (334) and by anticholinesterases (187). It is surprising that, in spite of the ability of anticholinesterase agents to stimulate and to abolish central respiratory activity, direct injection of acetylcholine into the medullary respiratory centers of the cat does not uniformly cause either respiratory stimulation or depression (82). However, considering that the actual location of the central chemosensitive cells has not been established (248), failure of administered acetylcholine to affect respiration in one location does not eliminate it as a possible central transmitter in some other portion of the complex central respiratory network.

Drugs Altering Efferent Impulses

With normal afferent and central mechanisms of respiratory control, drugs affecting efferent nerves or the neuromyal junction can alter respira-

tion or the response to respiratory stimuli. Such pharmacological influences have had essentially no quantitative study in animals or in man, although the qualitative effects of the mechanisms involved have received great attention. Tubocurarine has been used to study the respiratory response to exercise (291). The loss of respiratory responsiveness following administration of drugs such as curare (291) or intraspinal procaine should initially be masked by increased bombardment of the respiratory control mechanisms resulting from the combined stimulant effects of elevated P_{CO_2} and decreased P_{O_2} in the arterial blood. As with narcotic drugs, methods involving CO_2-ventilation response curves or maintenance of fixed, elevated alveolar P_{CO_2} should magnify and permit accurate, quantitative, and comparative study of the degree and time-course of the respiratory interference produced by neuromuscular blockade (223).

Hormones

Studies of the respiration of pregnant women led eventually to the suggestion that changes in the level of circulating progesterone influenced respiratory control. Fifty years ago (239) it was found that the alveolar P_{CO_2} of women was lower during pregnancy than following parturition. Supporting evidence that respiration is affected by hormonal factors in pregnancy and during menses has been provided over subsequent years (116, 117, 161, 162, 173, 175, 259). Alveolar P_{CO_2} is decreased during the luteal phase of the menstrual cycle. If pregnancy develops, the ventilation continues at an increased level throughout gestation, returning to normal only after delivery. Progesterone has also been found to be capable of producing increased ventilation in a menopausal woman (175) and in normal men (116, 117, 173, 175, 239).

Other agents which have been studied include prednisone (36, 90, 272), 16-methyleneprednisolone (Decortilen) (52), triamcinolone (304), and estrogen (161). Since other steroids having marked progestational activity are not found to increase ventilation, it has been presumed that some other property of progesterone is responsible for its respiratory stimulant action (376).

The stimulant properties of progesterone have been studied in patients with ventilatory disorders such as pulmonary emphysema where the efficiency of pulmonary ventilation is decreased (36, 52, 89, 90, 281, 376). Chronic administration of progesterone to hypercapneic, emphysematous patients produces an increase in alveolar ventilation and minute volume of respiration with a lowering of arterial P_{CO_2} (376) and a shift of the CO_2-ventilation response curve to the left (89, 175) without evident increase in slope. In one study (259) it was stated that an increase in slope of the respiratory response to CO_2 occurs in pregnancy and is produced by progesterone in normal men and menopausal women. It is possible that this apparently different result is due to the plotting of alveolar ventilation ratio rather than the more appropriate overall respiratory minute volume (227).

The observed effects of progesterone upon response to CO_2 could have been produced by influences upon the lung itself (52), by direct stimulation of central respiratory neurons, by a reflex action, or even by a general arousal mediated by effects upon central activating structures. The effect produced has been compared with the respiratory state of anxious psychiatric patients (272). In view of the fact that fluid retention and anxiety are recognized accompaniments of the premenstrual phase of the menses, this suggestion should be carefully considered. Possibly the precise measurement of respiratory reactivity may provide an indirect means of studying agents which modify the menstrual pattern.

An important but unsettled question is whether progesterone administration in normal and pathological states increases the sensitivity of respiratory neurons to CO_2 or merely changes the level of the central chemical respiratory stimulant. Doring et al. (117) have investigated and disclaimed the possibility that an elevation of body temperature produced by progesterone is responsible for the increased respiration. Moreover, no detectable change in arterial pH has been found to be produced by progesterone (89, 376). It should nevertheless be recognized that a fall in arterial Pco_2 in the absence of pH change in itself implies a metabolic acidosis, that respiration is grossly affected by very small changes in body temperature, and that changes in pH within the central nervous system may be more important than those in arterial blood.

TABLE V

CIRCUMSTANCES POTENTIALLY CAPABLE OF MODIFYING RESPIRATORY EFFECTS OF DRUGS

Unusual circumstance	References	Unusual circumstance	References
Fever	95	Hypoxia	6, 16
Hypothermia	119, 152, 354, 386	Hypocapnia	69
Sleep	40, 50, 148, 262, 314, 324, 339	Obstruction	75
Acidosis	6, 240	Prematurity of birth	88, 155, 171, 253, 366
Alkalosis	73, 199, 227	Aging	153, 186
Exercise	16	Obesity	333
Respiratory insufficiency	6, 58, 114, 124, 143, 369	Hormonal disorders	362, 377
		Pregnancy	162, 239
		Combined stresses	

Unusual Circumstances Affecting Respiratory Response to Drugs

It is evident that, like respiration itself, the respiratory responses to drugs such as those discussed in the previous pages are grossly modified by the physiological or pathological state of the experimental subject or animal. Since the pharmacology of respiration has only recently begun to be studied on a quantitative basis, the influences of many of the deviations from the normal resting state have yet to be studied. The modifying circumstances listed in Table V are cited, not because abundant information exists concerning their effects upon respiratory pharmacology, but because available information is inadequate, and because such information should be obtained. As an obvious example, the degree of respiratory depression produced by a narcotic drug in an excited, febrile, gravid female patient in pain can hardly be compared with that expected when the same dose of the drug is administered to a semicomatose, anoxemic, hypercapneic male with long-standing pulmonary emphysema.

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