MANUALLY ASSISTED AND CONTROLLED RESPIRATION:
ITS USE DURING INHALATION ANESTHESIA FOR
THE MAINTENANCE OF A NEAR-NORMAL
PHYSIOLOGIC STATE—A REVIEW

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PART I

It is the purpose of this review to show that controlled respiration
or its modification, assisted respiration (compensated, aided, aug-
mented, supplemented or reinforced), should be employed constantly
in almost all inhalation anesthesia because it effectively counters
the tendency of respiratory depressant and premedicant anesthetic
agents to cause hypoxia or respiratory acidosis or both. It is believed
that many complications during and following anesthesia are caused
by these two factors, hypoxia and hypercapnia. Seegers (1) said: “It
is probably true that a busy anesthetist, even the most expert, has dif-
culties with carbon dioxide almost every day of his life and uses narcotic
concentrations of this gas intermittently, or in some instances regularly,
whether he is aware of the fact or not.” Mousel (2) wrote in a similar
fashion that: “Very few anesthetics progress for more than a few
minutes in average hands without some degree of hypoxia under some
of the aforementioned headings (inadequate oxygen in the inspired air,
obstructed respiration, depression of the respiratory center by anes-
thetic overdosage, edema of the alveolar membrane because of hypoxia).”
There is a growing realization of the dangers that result from acute
or chronic oxygen deficit and carbon dioxide excess in mammalian tis-
sues. Continuous manual reinforcement of respiration, by rhythmic
intermittent pressure on the rebreathing bag of a closed system, cor-
rects this impairment of respiratory gas exchange from the action of
depressant agents upon the respiratory center or upon the reflexes
that control respiration. Nevertheless, the tendency is to make only
limited use of controlled or assisted respiration, that is, during intra-
thoracic operations, or when respiration is obviously depressed. We
believe the technic deserves wider use.

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Physiologic Factors Concerned in Breathing

Gordh (3) said recently: "The more the physiology of anesthesia is studied the more striking becomes the predominance of the part played by respiration. Indeed, the physiology of respiration may be said to dominate the physiology of anesthesia. Whereas during light anesthesia the respiratory reflex mechanisms, peripheral as well as central, are intact or at any rate barely affected, these reflexes are gradually depressed as the depth of anesthesia increases. When these reflex defense mechanisms are unduly depressed, the physiological stimuli of respiration, oxygen want and carbon dioxide excess, become depressant. The usual warning signals, so clearly shown in light anesthesia by increasing rate and depth of respiration, as well as by rising blood pressure, are absent in deep anesthesia, thus further endangering the already existent menace to life." Before considering the effects of anesthetics on the breathing process and their relation to controlled and assisted respiration, it would be well to review briefly the mechanism of normal breathing, factors related to pulmonary ventilation, problems associated with a closed system and the effects of oxygen and carbon dioxide excess and deficit.

The Respiratory Center

The respiratory center responds primarily to the tension of dissolved carbon dioxide in arterial blood and is depressed by hypoxia; a rise of the alveolar carbon dioxide tension by 1.5 mm. of mercury (0.2 per cent) will double the ventilation. Conversely, a reduction in alveolar carbon dioxide pressure depresses the respiratory center, and if excitatory stimuli are reduced to a negligible minimum, apnea results. Under optimum conditions apnea of brief duration may be produced by a fall in carbon dioxide pressure of 1.5 mm. of mercury. The respiratory response to carbon dioxide is not affected by denervation of the chemoreceptors, but mild hypoxia in such an animal or person may cause acute respiratory failure. It is important to note that the normal and dominant respiratory stimulus is carbon dioxide, a tissue waste product: first, because of its role in the maintenance of the hydrogen ion concentration of blood and extracellular and intracellular fluids, and second, by virtue of the fact that carbon dioxide diffuses more slowly within the alveoli than does oxygen, ventilation which is adequate to eliminate carbon dioxide as it is produced is more than adequate to replace oxygen in the alveolar air as the oxygen is absorbed. Ferris et al. (4) have determined on conscious subjects that the alveolar carbon dioxide tension is the chief determinant of ventilation when breathing air or oxygen-rich mixtures; the oxygen tension is an important respiratory stimulant only when breathing anoxic mixtures.
The chemoreflex control of respiration

The chemical control of respiration results from the stimulation of chemoreceptors in the carotid and aortic bodies by a reduced partial pressure of oxygen in the arterial blood; this control is resistant to moderate hypoxia but respiration will fail following exposure to severe hypoxia for any length of time. A reduction of the oxygen tension in the inspired air stimulates respiration, increasing rate, depth and minute volume (49); this increase in ventilation is not nearly as effective as that caused by carbon dioxide excess, where the increase is mainly owing to increase in depth of breathing. According to Dripps and Comroe (49), the anoxic stimulation of chemoreceptors in man plays no part in the control of respiration when breathing air at atmospheric pressure. A loss of carbon dioxide follows the increase in ventilation resulting from hypoxia, except during rebreathing, and serves to shift the control of respiration further from the center to the reflex control. The chemoreflexes act through the respiratory center, even though the latter may or may not be depressed by hypoxia or narcotics to its normal stimulus, carbon dioxide. Pi-Suner (6) believed that there are receptors in the bronchi and alveoli that are stimulated by carbon dioxide excess and whose afferent nerve fibers run in the vagus nerves to the respiratory center, but the role played by these in the control of respiration is unknown.

The Hering-Breuer Reflex

The Hering-Breuer Reflex causes slowing of respiration or apnea upon forced inflation of the chest, and stimulation of respiration upon forced deflation of the chest by suction. Of the reflexes that modify respiration, it is the most resistant to hypoxia. This reflex terminates inspiration during quiet breathing, thus accelerating the rate, but may augment inspiration in the deep breathing caused by exercise (see below). It prevents wide fluctuations in the composition of alveolar air, which would occur were respiration slower and deeper. This reflex is important during operation and anesthesia, for surgical pneumothorax, by collapsing the lung, tends to increase the rate and depth of breathing. On the contrary, continuous positive pressure breathing tends to slow the rate although recent work on man has shown that pulmonary ventilation may be increased. As will be shown, this reflex, like the chemoreflexes, is modified by the depth of anesthesia and the anesthetic agent in use.

Various types of sensory end organs within the tracheobronchial tree have been described. Larsell and Dow (7) have found them in the visceral pleura, various orders of bronchi out to the alveolar ducts, bronchial muscle, atria, perichondrium of the bronchial cartilage and adventitia of the pulmonary artery. Elftman (8) found sensory endings in the respiratory bronchioles, alveolar ducts and walls, at bifurca-
tions, in the bronchial musculature, and in the epithelium of the trachea, carina and major bronchi.

A division of function of afferent nerve fibers in the vagus nerve was first attempted by Adrian (9), when he found two types of fibers, one stimulated by inflation, the other stimulated by deflation. The inflation afferents faithfully mirror, by their impulse frequency, the degree of inflation of the lung, adapt slowly and remain sensitive to stretch long after circulation has ceased. Adrian believed that only the inflation afferents are normally stimulated during respiration. Knowlton and Larrabee (10, 11, 12) recently found four groups of respiratory afferent fibers in the vagus nerve of the cat, but none was stimulated only by deflation. One group with low threshold and slow adaptation is stimulated only by inflation and probably causes the Hering-Breuer reflex to inflation of the lung, and limits inspiration in eupneic or quiet breathing. A second group with low threshold and rapid adaptation is stimulated by both inflation and deflation and probably causes the usual reflex response to lung deflation. A third group, with high threshold to stretch and adapting rapidly, is stimulated only by inflation of the lung, and together with the second group causes a short inspiratory effort on excessive lung inflation but has no role in quiet breathing (it probably functions normally in yawning or the deep breathing associated with severe muscular effort). A fourth group with low threshold and slow adaptation is stimulated by both inflation and deflation but no function could be assigned to it. The action of lung inflation upon motor nerve impulses in single-fiber preparations of the phrenic nerve confirms these results upon afferent fibers.

It has been observed experimentally that the presence of hypoxia, carbon dioxide deficit or carbon dioxide excess during the demonstration of the Hering-Breuer reflex alters the response. Gordh (3) observed that hypoxia exaggerates the Hering-Breuer reflex, and that intense hyperpnea from carbon dioxide excess abolishes the reflex. The usual though not invariable respiratory reflex response to electrical stimulation of the vagus nerve consists in a decrease in ventilation, with increase in rate and decrease in depth, even to the point of apnea. Rice (13) noted that during carbon dioxide excess, stimulation of the vagus nerve causes an increase in ventilation owing to an increase in rate without a decrease in the depth of breathing. It has been shown that the increase in ventilation resulting from carbon dioxide excess is greater when the vagi are intact than when they have been cut. From these data it may be concluded that when respiratory alkalosis is present, whether due to voluntary or anoxic hyperventilation, the Hering-Breuer reflex is more active and tends to prevent adequate ventilation, which in turn permits carbon dioxide to accumulate and restore the normal hydrogen ion concentration of blood and tissue.

We have thought that a detailed account of the Hering-Breuer reflex is necessary in an analysis of respiratory control as pertains to
assisted and controlled respiration. We do not believe it to be necessary to describe in detail the role of the arterial pCO₂, pH and pO₂, and the intracellular pH of the respiratory center in the control of respiration, or the influences of the cerebral cortex during consciousness and the proprioceptive impulses from muscles, joint and tendons during anesthesia. The many factors that control respiration are considered in a provocative paper by Gray (13b), entitled: “The Multiple Factor Theory of the Control of Respiratory Ventilation.” The reader who desires a complete account of the organization of the respiratory center is referred to a review by Pitts (13a). Current developments in knowledge regarding the role of the chemoreceptor and other reflexes in the control of respiration under various conditions, including anesthesia, may be found in the Annual Review of Physiology, volumes I to X.

**Factors in Pulmonary Ventilation**

*Diffusion of Oxygen and Carbon Dioxide.*—Graham’s Law states that the rate of diffusion of one gas compared to another, in a gaseous medium, varies inversely as the square roots of their molecular weights; hence, if oxygen be assigned a diffusion rate of 1.0, carbon dioxide has a calculated diffusion rate of about 0.83 (14a). Nims (15, 16) noted that pulmonary gaseous exchange under normal conditions is not limited by diffusion through the alveolar and capillary membranes, but is determined by the diffusion of oxygen and carbon dioxide through the alveolar spaces. “The increase in volume of the lungs during inspiration occurs in the atria and the air passages; this mixes with normal capacity air and ultimately reaches the alveoli by gaseous diffusion. It may seem inefficient to aerate the blood, yet it serves to keep the composition of alveolar air nearly constant during the respiratory cycle.”

In support of the concept that carbon dioxide diffuses more slowly than oxygen within the alveoli, Moyer and Beecher (17) found that a minute respiratory volume of air sufficient to maintain a normal arterial oxygen content in animals anesthetized by evipal or pentothal may be insufficient to effect adequate removal of carbon dioxide. Stevens, Ferris et al. (4, 18) studied the changes in pulmonary volume which occur in man during breathing and concluded that oxygen diffuses out of the lung faster than carbon dioxide enters it, due both to the more rapid diffusion of oxygen in the alveolar air and to the removal of oxygen by circulating hemoglobin. This is not inconsistent with the fact that carbon dioxide passes through the alveolar membrane more rapidly than oxygen, because of the greater solubility of carbon dioxide in water and presumably in tissues; the diffusion coefficient for oxygen through pulmonary epithelium at rest is between 25 and 45, while that for carbon dioxide is about 500 (14). Stevens et al. emphasized that “breathing must be adjusted primarily to equilibrate the least diffus-
iable gas, namely carbon dioxide.” Others have observed that carbon dioxide tends to accumulate in the blood and alveolar air of conscious subjects when breathing oxygen-rich mixtures (5, 19); carbon dioxide accumulation is notable during anesthesia with cyclopropane and oxygen, as shown by Stormont et al. (20), Dripps (21), and Waters (22); it may occur as well under pentothal, ether and all the other respiratory-depressant anesthetic agents. The blood can be kept adequately oxygenated by “diffusion respiration” without external respiratory movements, following respiratory arrest from high pressures of oxygen (23), disease (24) or apneic doses of pentothal (25, 26, 27), yet there is a marked tendency for carbon dioxide to accumulate. Comroe and Dripps (24) observed two moribund patients kept alive by endotracheal insufflation of oxygen, in one of whom the alveolar carbon dioxide rose to 29.7 per cent, in the other to 44 per cent. Draper, Whitehead and Roth (25-27) noted during “diffusion respiration” in anesthetized dogs that the carbon dioxide reached narcotic levels, with an average concentration of 54.7 per cent in the alveolar air after forty-five minutes of “respiration” by diffusion. They thought that ultimately the carbon dioxide may exclude oxygen from the lungs during “diffusion respiration” in the absence of mechanical ventilation. It is of interest to us, in defense of the philosophy of assisted respiration, that they believed the recovery from anesthesia was delayed owing to the narcotic concentrations of endogenous carbon dioxide.

Effects of Increase in Ventilation.—Each breath at rest replaces about one-seventh of the air that remains in the lungs after a normal quiet expiration; the ventilation of the lungs is improved by those factors which increase the tidal volume. Increased ventilation serves to improve the oxygenation of arterial blood and the removal of carbon dioxide (28); the alveolar oxygen tension is raised in proportion as the alveolar carbon dioxide tension falls. A similar mechanism to raise anesthetic tensions in the lungs, using either manual augmentation or hyperventilation resulting from carbon dioxide excess, may be used to hasten induction or emergence with gaseous or volatile anesthetic agents. There is widespread agreement that difficulties of ventilation occur in silicosis, pulmonary tuberculosis and hypertrophic emphysema because of unequal distribution of the tidal air, some or many of the alveoli being hypoventilated. An additional factor in emphysema may be a defective capillary network over the dilated alveoli (29, 30, 31, 32). Manually-increased ventilation in these conditions may help correct mechanical difficulties in the ventilation of these patients, but will not benefit deficiencies in gas transport owing to thickened alveolar membranes or defective pulmonary circulation.

Relation between Respiration and the Flow of Blood and Lymph.—Physiologists have long talked of the “respiratory pump” action of the movements of breathing: descent of the diaphragm during inspiration lowers the intrathoracic pressure in comparison with the extrathoracic
pressure (which favors return of venous blood), and compresses abdominal viscera, which massages blood back into the inferior vena cava and towards the heart. Inspiration increases the amount of blood in the right auricle and ventricle relative to that in the left auricle and ventricle, by aspiration of blood from the great veins into the pulmonary circuit (33); this is reflected in a slight fall in systemic blood pressure. The inflow of blood into the left auricle and ventricle is increased during expiration and is the result of the elastic expulsive force of the lungs during expiration upon the blood in the pulmonary veins (33, 34, 35). Accordingly, expiration is associated with a slight rise in systemic blood pressure. Other investigators (36, 37, 38) have observed that positive intrathoracic pressures created by coughing, dying gasps or artificial respiration, may propel blood through the lungs and into the aorta even after cardiac arrest. Nevertheless, the suspension of respiratory movements by the Thunberg “barospirator” (39), by endotracheal insufflation anesthesia, by apneic doses of barbiturates combined with diffusion respiration, or by apneic doses of curare in man, has had no marked effect upon the blood pressure, heart rate and venous pressure (the effects of pressure breathing upon the circulation are discussed below).

Drinker (40) has clarified the relationship between respiration and pulmonary lymph flow. As in other tissues throughout the body, hypoxia causes an increase in capillary permeability and an increased formation of interstitial fluid; in the lung, the increase in interstitial fluid which follows breathing air deficient in oxygen leads to still further anoxic formation of interstitial fluid by interfering with ventilation of alveoli and by obstructing the diffusion of oxygen and carbon dioxide between the alveoli and pulmonary capillaries—a veritable vicious circle. Carbon dioxide hyperpnea increases the pulmonary lymph flow, which is partly attributed to an increased negative intrapleural pressure. Inspiratory obstruction increases lymph flow by a similar mechanism, and is a well-known cause of pulmonary edema. The hyperpnea associated with muscular effort may cause pleural effusions. Expiratory obstruction and positive intrapulmonic pressure in general give extravascular support, cause a temporary increase in lymph flow by drying out the tissues and then a reduction in lymph flow.

The Effect of Posture on Pulmonary Ventilation.—Altschule (41) showed that the Trendelenburg position reduces the vital capacity by decreasing the supplemental air (but increases the complementary air owing to the cephalic shift of the diaphragm); atelectasis is favored by the decrease in supplemental air, which may reduce the lung volume about 20 per cent. Case and Stiles (42) measured the vital capacity of normal conscious subjects in various surgical positions and found it to be 100 per cent when sitting, 91 per cent when supine, 90 per cent when prone, 88 to 90 per cent when lateral; 85 per cent with the kidney lift in position, 85 per cent in the Trendelenburg position and 82 per
cent in the lithotomy position. Somewhat similar values were obtained by Stephen (43). In spite of a reduced vital capacity in the Trendelenburg position, the minute volume of respired air in some cases may be increased over that present in the horizontal or Fowler's positions, but this depends in part upon the anesthetic agent and the activity of the Hering-Breuer reflex (3). Slocum et al. (43a) have shown dramatically how certain surgical positions may embarrass the respiration of anesthetized patients. Vaccarezza et al. (44) showed bronchospirometrically that the inferior lung in the lateral position has a smaller volume than when uppermost or supine, shows a greater change in volume with respiration (owing to "elastic hypotension"), takes a greater share in ventilation (with increased oxygen intake, minute volume, vital capacity and complementary air), and costal respiration is decreased on the lower side but diaphragmatic motion is increased. The "decubitus lateralis represents for the homolateral (dependent) lung a position of greater rest notwithstanding the increase in the respiratory ventilation of the same." It is noteworthy that Faulconer et al. (45) observed atelectasis in 8 of 85 operations upon the upper urinary tract. In each case the atelectasis was contralateral to the side of operation and was attributed to the kidney rest and to splinting of the dependent lung by the lateral position.

Drinker (40, 46) observed a tendency for atelectasis to develop in the posterior, less well-ventilated areas of the lungs of animals anesthetized and kept in the supine position for prolonged periods. He noted that the signs of onset of atelectasis may be masked by the use of oxygen-rich mixtures because of the large reserve of lung tissue which is not ordinarily employed during rest or under anesthesia.

Of interest is the fact that tidal volume is lower (in conscious subjects) in the sitting, both lateral and both kidney positions, than in the supine position, and is higher in the Trendelenburg position. The minute volume is decreased in the reverse Trendelenburg, both kidney, and in the gallbladder positions as compared to the supine position; the maximum breathing capacity is also decreased in these positions (211).

**Physiologic Problems Associated with a Closed System**

Jackson (47) introduced the carbon dioxide absorption technic into laboratory experimentation in 1915 and found it to be applicable to nitrous oxide, ethyl chloride, ether, chloroform, ethyl bromide, somnform and so forth. Waters applied it to clinical anesthesia in 1923. Its advantages are: conservation of expensive anesthetic agents, retention of body heat and water, restriction of explosive agents and a quiet shallow type of breathing which facilitates some surgical procedures.

A closed system tends to cause respiratory acidosis because it always increases the dead air space, said by some to be greater in the to-
and-fro type than in the circle type; the effect is minimized by using endotracheal tubes (14). In relation to the tidal air of a child, the mechanical dead space imposed by a mask may be so great that carbon dioxide accumulation because of rebreathing can be prevented only by endotracheal anesthesia or by insufflation.

The carbon dioxide absorption technic also determines which agents may be used; the ethers, cyclopropane, ethylene and nitrous oxide are not affected by the soda lime; chloroform and ethyl chloride are partially decomposed by the soda lime but the products are absorbed; trichlorethylene cannot be used in a closed system because it reacts with soda lime to form toxic dichloro-acetylene. Nitrous oxide is difficult to use in a completely closed system because of its lack of potency, the difficulty in exactly supplying maintenance oxygen and the elimination of nitrogen early in the anesthetic period.

The Effects of Oxygen and Carbon Dioxide Excess and Deficit

Oxygen Excess has little significance to anesthesia except when it may help cause respiratory depression when given during barbiturate or cyclopropane anesthesia; oxygen-rich mixtures may be used to help avoid overdosage with evipal, pentothal, avertin and cyclopropane by abolishing the chemoreceptor (or hypoxic) control of respiration (49), which may be less depressed by these agents than is the respiratory center, for with high oxygen tensions, overdosage as shown by respiratory depression is apparent sooner. Prolonged breathing of 100 per cent oxygen produces toxic effects on the central nervous system, lungs and heart, which apparently are the result of the destructive action of high oxygen tensions upon certain unidentified enzyme systems (50).

In relation to the use of oxygen-rich mixtures, Waters (51) remarked that: “The practice of administering as a matter of routine an oxygen atmosphere rather than an atmosphere of nitrogen and only sufficient oxygen has undoubtedly resulted in frequent untreated physiologic disturbances and unrecognized obstruction and depression of breathing.”

Carbon Dioxide Lack produces effects the interpretation of which is controversial. Henderson thought years ago that lack of carbon dioxide could lead to shock and death, but this has been shown to be owing to an associated excessive depth of anesthesia. Seevers et al. (52, 53) mechanically hyperventilated anesthetized dogs for as long as fifteen hours with but one death (from lung rupture). The arterial carbon dioxide tension may fall to 5 mm. of mercury and the tissue carbon dioxide to 9 mm. of mercury. The arterial pressure fell 10 to 50 per cent of the initial value on beginning the hyperventilation, proportional to the depth of anesthesia, but returned to normal or above as hyperventilation continued. Similar results were obtained on anes-
thetized patients, the arterial carbon dioxide tension falling to 9 or 10 mm. of mercury and the pH rising to 7.71 or 7.73, with a fall in plasma bicarbonate; the blood pressure fell 8 to 25 mm. of mercury, average 10 mm., with this severe hyperventilation. Apnea lasted two to nine minutes upon cessation of the hyperventilation. They believed that "The adverse effects of respiratory alkalosis on the circulation or on the general vitality, even during anesthesia, have been overemphasized."

Voluntary forced respiration in normal human beings generally causes a fall of blood pressure which is attributed in part to the effect of forced expiratory movements upon the venous return to the heart, and to the effect of acapnia upon the vasomotor center (54); nevertheless, Barach et al. (55) observed that circulatory collapse from hyperventilation occurred only in those with vasomotor instability. Bernthal (56) perfused the carotid bodies of animals with solutions containing low tensions of carbon dioxide, which led to a fall in blood pressure through reflex vasodilatation; solutions containing high tensions of carbon dioxide caused a rise in blood pressure. While the chemoreceptors may constitute one source of tonic chemoreflex vasoconstrictor influence, in response to the arterial pCO₂, this same stimulus to the chemoreceptors has little or no effect on respiration.

In part due to the acapnia caused by hyperventilation, the cardiac diastole becomes less complete, the venous pressure falls and the A-V conduction rate increases; the heart rate rises because of increased sino-auricular nodal activity. Some of the electrocardiographic changes that are associated with hypoxia are probably the result of carbon dioxide lack, since they may be prevented by added carbon dioxide.

Carbon dioxide lack removes the chief stimulus for normal breathing and prolonged apnea may follow hyperventilation with oxygen. Respiratory failure under hypoxia is caused partly by associated carbon dioxide lack.

Carbon dioxide lack has a significant effect on the cerebral circulation and mental processes. Barach et al. (55) reported that cerebral efficiency decreases when the alveolar carbon dioxide is lowered 10 mm. below normal, and that rapid mental depression occurs when the alveolar carbon dioxide falls below 23 mm. of mercury, even in the absence of hypoxia. The possibility remains to be investigated that acapnia contributes to the depth of anesthesia or improves relaxation. Acapnia, by causing cerebral vasoconstriction, may reduce the cerebral blood flow 30 per cent. Although hypoxia causes cerebral vasodilatation, the effects of acapnia and hypoxia are additive rather than antagonistic in regard to mental performance tests (57). The loss of consciousness and electroencephalographic changes due to hypoxia are partly the result of respiratory alkalosis, for they may be prevented in part by added carbon dioxide in the inspired atmosphere.
The possibility has been raised by Carreyer (58), as well as by others, that tissue hypoxia may result when the blood becomes sufficiently alkaline from hyperventilation, and that it may produce symptoms characteristic of voluntary hyperventilation, hypoxia from high altitudes and occlusion of the coronary artery. This may happen because increased alkalinity of the blood shifts the oxygen-hemoglobin dissociation curve "to the left," which results in the hemoglobin clinging to the oxygen more tenaciously, or in giving up the usual amount of oxygen only when the tissue oxygen tension falls below the normal value. Tissue hypoxia may also occur because of the decreased blood flow which follows vasoconstriction resulting from local tissue acapnia. The interrelationships between hypoxia, acapnia and increased blood alkalinity are not simple or clear, and are further complicated by newer data relating to the direct role of carbon dioxide in respiration and tissue metabolism. It would seem to be unlikely that mild alkalosis or acapnia can have any serious effect on utilization of tissue oxygen.

_Hypoxia_, of one form or another, is frequently present during anesthesia, and probably causes some of the postoperative symptoms, as anxiety, delirium, weakness and so forth. Hypoxic signs may develop during the anesthesia and be carried over into the postanesthetic period: increased or depressed respiration; rise or fall of blood pressure; increase in pulse rate; muscular incoordination; twitching; convulsions; cyanosis; signs of temporary or permanent cerebral damage; decrease in gastric motility and delay in gastric emptying and postoperative nausea and vomiting. Hypoxia primarily depresses the spinal cord and brain, including the respiratory and vasomotor centers; the chemoreceptor and vagal reflexes governing respiration and circulation are much more resistant. The respiratory stimulation caused by hypoxia tends to increase the alveolar oxygen tension at the expense of the alveolar carbon dioxide tension.

_Carbon Dioxide Excess_ occurs frequently in anesthesia from a number of factors and, while acute carbon dioxide excess is not as harmful to the patient as acute hypoxia, it has widespread actions. This condition is the one that is most amenable to correction by manually-assisted respiration, and is the object of this review. Carbon dioxide excess causes an increase in ventilation and in blood pressure in mild excess, and a fall of blood pressure and failure of respiration in severe excess, with the respiratory center failing before the vasomotor center. The effect on the central nervous system results in depression, headache, nausea, dizziness, unconsciousness, twitching, muscle spasms and convulsions, and surgical anesthesia.

In addition to the customary effect of carbon dioxide excess on respiration and blood pressure, two types of response under anesthesia indicate toxic concentrations of carbon dioxide: (1) pallor with simulated collapse, low blood pressure and slow pulse; depressed, gasping
respiration; (2) muscular activity with twitching of facial muscles, if associated with absence of respiratory stimulation (85).

The respiration is increased, chiefly in depth, by carbon dioxide excess, and a normal alveolar carbon dioxide tension can be maintained as the inspired concentration increases up to 5 per cent; respiratory stimulation increases up to a concentration of about 10.4 per cent (59), above which it gradually decreases until respiration is normal or depressed at a concentration above 30 per cent, owing to the increasing narcotic effect with higher concentrations.

The A–V conduction of the heart is depressed by a rise in the hydrogen ion concentration which results from carbon dioxide excess, and complete block occurs at pH 7.0 (54). The S–A node is depressed also, which tends to slow the rate and may cause irregular rhythms. As with hypoxia, circulatory failure is due to heart failure and not to failure of the vasomotor center.

The rise in blood pressure is mainly the result of the stimulation of the vasoconstrictor center in the medulla. The pressure rises as the concentration rises to 30 per cent, then returns to normal and is depressed with concentrations above 40 per cent. The pressor tendency may be weakened or masked completely under anesthesia. Dripps (21) in an analysis of “cyclopropane shock” found that the postoperative fall in blood pressure was related to the arterial tension of carbon dioxide during operation and its subsequent fall to a normal level with termination of the anesthesia. It would appear that the excess carbon dioxide is lost more rapidly than compensatory blood pressure reflexes recover from the anesthetic agent so that hypotension develops in a manner similar to that observed during mechanical hyperventilation of anesthetized patients or animals. There may be other factors as well. Seevers (1) believed that anesthetics or coincident disease may impair the ability of the body to compensate to excess carbon dioxide, and that some of the postanesthetic signs and symptoms may be caused by previous carbon dioxide excess, acid-base and other compensatory changes, return of sensitivity of the respiratory center to carbon dioxide, and a relative carbon dioxide deficit at the end of anesthesia.

Waters noted that the inhalation of 5 to 6 per cent carbon dioxide for several hours is followed by a headache lasting several hours. Ten per cent carbon dioxide is the maximum concentration that can be inspired by human beings without stupefaction. Seevers (1) believed that all concentrations above 5 per cent possess some depressant qualities, even though such effects may not be readily detected by ordinary means. Leake and Waters (60, 61, 62) observed that 10 to 20 per cent carbon dioxide failed to anesthetize small animals readily but caused a marked rise in blood pressure. Thirty to forty per cent carbon dioxide anesthetized dogs and small mammals in about sixty seconds without struggling, with an initial rise in blood pressure but normal pressure and deep respiration during anesthesia; convulsions were
likely to occur after ten to fifteen minutes. The heart and respiration were depressed by concentrations above 40 per cent. Crafoord (63, 106), in developing a basis for the use of controlled respiration in intrathoracic surgery, found that a continuous rise in alveolar carbon dioxide occurred in animals with a surgical pneumothorax and breathing oxygen under continuous positive pressure; when the alveolar carbon dioxide reached 60 volumes per cent (the mechanism of accumulation is noted above), the need for anesthesia disappeared owing to the narcotic effects of high concentrations of carbon dioxide. Crafoord cited an experiment by Volhard in which curarized dogs were kept alive by endotracheal insufflation of oxygen, but death occurred in one and a half to two hours, when the alveolar carbon dioxide had reached 80 to 90 per cent.

It has been observed by Barbour and Seevers (1, 64) that 10 per cent carbon dioxide lowers oxygen consumption, and 5 per cent carbon dioxide at 5 C. is sufficiently narcotic to cause a condition resembling hibernation in rats and dogs.

Concentrations of carbon dioxide of 40 per cent and above in some experimental animals may cause pulmonary edema, hemorrhages from exposed mucous membranes and death in a short time.

It must be noted that Cassels, Becker and Seevers (65) believed that convulsions during anesthesia are due to the summation of several factors, each of which is incapable of causing convulsions by itself: youth, pyrexia and carbon dioxide excess.

**Pharmacologic Actions of Anesthetic Agents**

"During clinical anesthesia, disturbed physiologic and biochemical functions are the rule rather than the exception. They are regularly reflected in altered respiratory movements" (66).

In tables 1 and 2 an attempt is made to summarize the effects of some of the commonly used anesthetic agents and narcotic drugs upon the respiratory center, the chemoreceptors in the carotid and aortic bodies, the Hering-Breuer receptors and reflex and the bronchiolar musculature. It may be noted (67): "The balance between chemical and nervous factors in respiratory control is disturbed by narcotic drugs, but the degree and even the type of the disturbance vary according to the drug, perhaps also according to the individual. The single common result of all narcotics in all individuals is a decrease in the sensitivity of the respiratory center to increased carbon dioxide in the blood (except with nitrous oxide). . . . Another almost constant result of all the narcotics so far tested is decreased respiratory minute volume, which results from all of them except ether (and nitrous oxide). . . . Another quite common, though by no means constant result of narcotics is to shift the balance of factors involved in respiratory control to the carotid and aortic reflex system. . . . The barbiturates and morphine apparently do exactly this. . . . Among the drugs so far studied only cyclo-
### TABLE 1

**Pharmacologic Effects of Some Anesthetic Agents on the Control of Respiration**

Respiratory Center (Stimulus is an increased pCO₂ of the arterial blood; center is depressed by hypoxia)

<table>
<thead>
<tr>
<th>1. Response to CO₂</th>
<th>Ethyl Ether</th>
<th>Evipal, Pentothal, other B.A. Deriv.</th>
<th>Cyclopropane</th>
<th>Nitrous Oxide</th>
<th>Chloroform</th>
<th>Trichlorethylene</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to CO₂</td>
<td>Depressed</td>
<td>Depressed, lost in deep anesthesia. CO₂ may become depressant</td>
<td>Depressed, marked accum. of CO₂ even with a closed system</td>
<td>Response is preserved; depressed by concurrent hypoxia</td>
<td>Depressed</td>
<td>Probably depressed</td>
<td>Depressed or lost</td>
</tr>
<tr>
<td>2. Action on Center</td>
<td>Increased min. vol. in light anesthesia. Center remains dominant, all planes</td>
<td>Decreased min. vol., progressive shift of control to chemoreflexes, with incr. depth</td>
<td>Progressive depression without initial stimulation</td>
<td>Stimulation by release from cortical inhibition</td>
<td>Min. vol. may be increased in light anesthesia as with ether</td>
<td>Rapid, shallow breathing in deep anesthesia, due to H-B reflexes</td>
<td>Respiration is depressed</td>
</tr>
<tr>
<td>3. Site of &quot;Vagotomy&quot;</td>
<td>Centrally, on inspiratory half center; perhaps peripherally</td>
<td>Vagotomy does not occur</td>
<td>Probably at respiratory center</td>
<td>Vagotomy does not occur</td>
<td>Probably at respiratory center</td>
<td>Vagal reflexes not depressed</td>
<td>Vagotomy does not occur</td>
</tr>
<tr>
<td>4. O₂-rich Mixtures</td>
<td>No effect on respiration</td>
<td>Causes &quot;oxygen-apnea&quot; in deep anesthesia</td>
<td>May slightly depress respiration</td>
<td>&quot;Oxygen-apnea&quot; indicates serious hypoxia</td>
<td>Probably no effect on respiration</td>
<td>May cause &quot;oxygen-apnea&quot;</td>
<td></td>
</tr>
<tr>
<td>5. References</td>
<td>3, 68, 68a, 69, 70</td>
<td>3, 68, 68a, 71, 72</td>
<td>21, 60</td>
<td>21, 81</td>
<td>49, 68, 68a, 69, 82</td>
<td>68, 68a, 70</td>
<td>72, 74</td>
</tr>
</tbody>
</table>

Chemoreflexes (Carotid and aortic bodies; stimulus is a decreased pO₂ of the arterial blood)

<table>
<thead>
<tr>
<th>1. Response to Hypoxia</th>
<th>Ethyl Ether</th>
<th>Evipal, Pentothal, other B.A. Deriv.</th>
<th>Cyclopropane</th>
<th>Nitrous Oxide</th>
<th>Chloroform</th>
<th>Trichlorethylene</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response depressed with incr. depth, more so than center to CO₂</td>
<td>Not depressed; hypoxia is main respiratory stimulus in deep anesthesia</td>
<td>Carotid body reflexes depressed; no compensatory reflex drive</td>
<td>Normal, not depressed</td>
<td>Response to hypoxia is abolished in deep anesthesia</td>
<td>Normal or exaggerated. Hypoxia dominates control of respiration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. References</td>
<td>3, 67, 70, 73, 74, 75</td>
<td>3, 17, 67, 70, 71</td>
<td>49, 67, 70</td>
<td>81, 84</td>
<td>73, 83</td>
<td>67, 70, 74</td>
<td></td>
</tr>
</tbody>
</table>
**TABLE 2**

**Pharmacologic Effects of Some Anesthetic Agents on the Control of Respiration**

**Hering-Breuer Receptors and Reflex (Stimulus is inflation and deflation of the lung)**

<table>
<thead>
<tr>
<th></th>
<th>Ethyl Ether</th>
<th>Evipal, Pentothal, other B.A. Deriv.</th>
<th>Cyclopropane</th>
<th>Nitrous Oxide</th>
<th>Chloroform</th>
<th>Trichlorethylene</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Action</strong></td>
<td>Inflation and deflation receptors initially more excitable; impulse frequency ineq, 30 to 100%; accompanied by simultaneous depression, with loss of response from 20-25% ether vapor</td>
<td>Inflation receptors show transient decrease in impulse frequency to inflation of lung, under nembutal</td>
<td>Receptor impulse frequency ineq, 50-100%, without any depression at any concentration</td>
<td>Inflation receptors more sensitive, as with cyclopropane; sense organs resistant to absolute anoxia</td>
<td>Initial exaggeration of response, with depression under 1% vapor; loss of excitability from vapor concentration of 3.5%</td>
<td>Inflation receptors show 30-140% increase in impulse freq, under 1-2% vapor; beginning depression from more than vapor, loss of response with 5.5% vapor. Depression receptors show only exaggeration of response, without depression</td>
<td></td>
</tr>
<tr>
<td><strong>2. Action</strong></td>
<td>Active reflex in light anesthesia; is abolished in deeper planes both by peripheral action on receptors and by &quot;central vagotomy&quot;</td>
<td>Reflex is exaggerated because of depression of resp. center to CO2 and by pharmacologic &quot;decrabation&quot;</td>
<td>Reflex abolished in deeper planes, by action of agent on respiratory center (&quot;central vagotomy&quot;)</td>
<td>Reflex is present under all concentrations of nitrous oxide</td>
<td>Reflex response to inflation and deflation of lung is abolished by surgical anesthesia</td>
<td>Rapid, shallow breathing in deep anesthesia believed due to action on H-B receptors</td>
<td>Reflex is present or exaggerated; first shown on dogs under morphine anesthesia by Hering and Breuer in 1866</td>
</tr>
<tr>
<td><strong>3. References</strong></td>
<td>3, 68, 68a, 71, 76, 77</td>
<td>3, 68, 68a, 71, 76, 77</td>
<td>68, 68a, 71, 76, 77</td>
<td>68, 68a, 76, 77</td>
<td>3, 9, 68, 68a, 76</td>
<td>68, 68a, 76</td>
<td>3, 13a</td>
</tr>
</tbody>
</table>

**Action on Bronchi**

<table>
<thead>
<tr>
<th></th>
<th>Ethyl Ether</th>
<th>Evipal, Pentothal, other B.A. Deriv.</th>
<th>Cyclopropane</th>
<th>Nitrous Oxide</th>
<th>Chloroform</th>
<th>Trichlorethylene</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Action</strong></td>
<td>Dilatation</td>
<td>Moderate to marked constriction</td>
<td>Constriction</td>
<td>Slight constriction</td>
<td>Dilatation</td>
<td>Dilatation</td>
<td>Weak constriction</td>
</tr>
<tr>
<td><strong>2. Mechanism of action</strong></td>
<td>1. Smooth muscle depression; vagal stimulation; prevented by atropine and epinephrine</td>
<td>Vagal stimulation; prevented by atropine and epinephrine</td>
<td>Direct stimulation of bronchial smooth muscle</td>
<td>1. Smooth muscle depression; vagal paralysis, sympathetic stim.</td>
<td>Vagal stimulation, prevented by atropine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. References</strong></td>
<td>79, 80</td>
<td>79</td>
<td>79</td>
<td>79</td>
<td>70, 80</td>
<td>79</td>
<td>79</td>
</tr>
</tbody>
</table>

Manually Assisted and Controlled Respiration

propane is uniformly depressant and evokes no compensatory reflex drive. This gas depresses the response of the center to carbon dioxide (as all narcotics do), interferes drastically (like ether) with the effectiveness of reflexes from the carotid and aortic bodies (which would not be activated in any case because of the high oxygen tension with which cyclopropane is routinely given) and does not set up any reflexes (as ether does) because it is non-irritant. Perhaps this explains why paralysis of respiration occurs earlier in anesthesia by cyclopropane than by any other agent now in use.

The Respiratory Center

Table 1 shows that of the narcotic agents listed (true also of unlisted agents), only nitrous oxide, when given without hypoxia, does not depress the sensitivity of the respiratory center to carbon dioxide. There is a wide variation in the ability of various narcotics to depress the sensitivity of the respiratory center, for the property of a given agent to depress respiration is probably independent of the property to produce anesthesia or analgesia. It may be generalized that the ease of producing controlled respiration with a given anesthetic agent varies directly with the degree of respiratory center depression. Severe degrees of respiratory acidosis may result from nonirritant agents like cyclopropane and pentothal, but are less likely to occur with ether and other respiration-stimulating agents. Using a closed technic with cyclopropane, blood carbon dioxide tensions between 42 and 120 mm. of mercury and blood pH values of 6.99 to 7.37 have been recorded on anesthetized man (21, 22, 48). Seevers (1) noted that a blood pCO₂ of 75 to 80 mm. of mercury is equivalent to 10 to 11 per cent carbon dioxide in the alveolar air, though normally the arterial pCO₂ is approximately 40 mm. of mercury (5.5 per cent).

Divinyl ether and ethyl chloride affect respiration in a manner like that of diethyl ether (49, 85); however, the effect of n-propyl methyl ether on respiration is more like that of cyclopropane than of diethyl ether (86). Pentobarbital depresses the response to carbon dioxide (72). Chloralose in large doses may abolish the sensitivity to carbon dioxide but in "increases" the sensitivity of the chemoreceptors to cyanide (74). Deep urethane anesthesia abolishes the response to carbon dioxide (87). Chlorbutanol depresses the response of the respiratory center to carbon dioxide but depresses the chemoreflexes more strongly and may abolish their responses (72). Meperidine has little effect on respiration in therapeutic doses, but some of the new piperidine derivatives related to meperidine are potent respiratory depressants. Curare apparently isolates the respiratory center from incoming afferent stimuli, for in the period before peripheral paralysis is noted, central sciatic or vagus nerve stimulation has no effect on respiration (88).
Although ethyl ether, vinethene, ethyl chloride and chloroform depress the response of the respiratory center to its usual stimulus, carbon dioxide, hypoxic stimulation of chemoreceptors (in animals) is not an important factor in the control of respiration during anesthesia with these drugs. This is so either because they may be administered with oxygen or because respiratory stimulation through various means suffices to keep arterial oxygen tensions near normal levels. Such stimulation may be the result of direct stimulation of the respiratory center by the agent (49, 68); irritation of the respiratory mucosa and possibly of the Hering-Breuer reflex mechanism (49, 69, 83); afferent impulses originating in the muscles, joints and tendons of the extremities from the presence of ether in the blood stream (49).

The popularity of nitrous oxide-oxygen-ether anesthesia may as well be due to the lack of respiratory depression with nitrous oxide and the lack of marked depression with ether as to its flexibility.

**The Chemoreflexes**

Although information is lacking on the subject, it may be possible that the chemoreceptors and the chemoreflexes are each affected differently by anesthetics just as the pulmonary inflation and deflation receptors and the Hering-Breuer reflexes may be affected differently (see below). Table 1 shows that ether, cyclopropane and chloroform depress the chemoreflexes, that nitrous oxide has no action on them, and that morphine, pentothal and evipal "accentuate" them. Respiration under the last three agents may be controlled chiefly by the chemoreflexes. Agents not included are: tribromethanol and pentobarbital, which exaggerate the reflexes (49, 72); chlorbutanol, urethane, paraldehyde and alcohol, which markedly or completely depress the chemoreflexes (72) and chloralose, which "sensitizes" the chemoreflexes to the stimulating action of excess carbon dioxide, hypoxia and cyanide (70, 72, 74).

Dripps and Dumke (70) studied the effects of morphine, barbital, nembutal and pentothal on cats and dogs, and observed instances in which some of these drugs appeared to exaggerate the responses of the chemoreceptors to cyanide. The exaggerated responses were shown to be caused by coincidental hypoxia, resulting from the depression of respiration with these narcotics; when hypoxia was prevented, the chemoreceptor sensitivity, as judged by a test dose of sodium cyanide, was unchanged. On the other hand, ether and cyclopropane diminish the chemoreflex response to hypoxia and cyanide and, with ether, presumably because of a depression of nerve impulse transmission within the central nervous system.

The phenomenon of "oxygen apnea" was first described by Marshall and Rosenfeld (72) and illustrates the role that hypoxic stimulation may have in controlling respiration under barbiturate or morphine anaesthesia; when hypoxia becomes the chief respiratory stimulus with
these agents, a breath of oxygen, to eliminate chemoreceptor control, will depress respiration or cause a brief apnea. Moyer and Beecher (17, 89) and others (25, 26, 27) have noted that during oxygen apnea or when breathing is depressed because of administration of oxygen during barbiturate anesthesia, carbon dioxide accumulates to high, narcotic and possibly fatal levels.

The Hering-Breuer Reflex (see table 2)

An attempt has been made by Whitteridge and Bulbring (68, 68a, 76) to correlate the action of the various anesthetics upon respiration in clinical practice with the effect of the anesthetics upon the pulmonary sense organs which are responsible for the Hering-Breuer reflex in the cat. They believed their results explain the characteristic rapid and shallow breathing under trichlorethylene and may explain the shallow respiration under cyclopropane. Likewise, Schmidt (69) believed that the Hering-Breuer reflex is concerned, although indirectly, in the respiratory stimulation that occurs in Plane I and II of ether anesthesia.

Whitteridge and Bulbring observed that all volatile or gaseous anesthetic agents (nitrous oxide, cyclopropane, trichlorethylene, chloroform, ethyl ether, divinyl ether and ethyl chloride) increase the excitability of the pulmonary receptors that are stimulated by inflation; this increases the frequency of respiratory afferent nerve impulses in the vagus nerve by 30 to 140 per cent over the usual frequency during similar inflation with air. The sensitization is accompanied or followed by a depression with all agents except the two gases, proportional to the concentration of the agent, so that sensory "adaptation" occurs to a continuing inflation with reduction in the impulse frequency or complete cessation of response; these receptors ordinarily adapt very slowly to continuous inflation. The depression increases with increasing concentration of the anesthetic vapor until the receptors may fail to respond at all to inflation. With ethyl ether, total depression of the inflation sense organs occurs with a vapor concentration considerably below that causing respiratory arrest. On the other hand, failure of response to inflation when using chloroform or trichlorethylene occurs with vapor concentrations which cause respiratory arrest. Ethyl chloride was found to be the most depressant to the pulmonary receptors, followed in decreasing order by chloroform, ethyl ether, divinyl ether and trichlorethylene. One hundred per cent nitrous oxide and cyclopropane produces only sensitization without concurrent depression. Pentobarbital produces a transient decrease in the sensitivity of the inflation receptors while chloralose has no action on them. The deflation receptors are first sensitized then depressed by chloroform and ethyl ether, but show only sensitization with trichlorethylene.

These results do not entirely explain the activity of the Hering-Breuer reflex under anesthesia. The reflex is exaggerated under barbituric acid derivatives yet they depress the activity of the receptors.
Cyclopropane and ether sensitize the inflation receptors (ether has a depressant action as well), yet they abolish the reflex apnea caused by lung inflation in sufficiently deep planes of anesthesia (90). Chloroform, ether and urethane (3, 82) are said to produce a "central vagotomy," the first two probably producing a synaptic block at the central endings of the inflation afferent nerve fibers of the vagus nerve on the inspiratory half center in the medulla; nevertheless, the work of Whitteridge and Bulbring (68, 68a) previously cited may indicate that a "peripheral" vagotomy also occurs when using ether. Pentothal does not have this central action for, although it depresses the respiratory center like ether and chloroform, it exaggerates the Hering-Breuer reflex by reason of producing a pharmacologic decerebration (3) and by its depression of the respiratory center.

The Hering-Breuer reflex has clinical application during anesthesia. Morton (77) measured the force developed by expiration and the force required to move both thorax and abdomen upon manual inflation of the chest. The pressure developed on expiration is increased by good health, a large tidal volume premedication with atropine, nitrous oxide or light ether anesthesia and carbon dioxide accumulation; it is decreased in the debilitated or during shock, by a small tidal volume, by respiratory depression from morphine or avertin, or during anesthesia with barbiturates, cyclopropane or deep ether. These results are attributed to the activity of the Hering-Breuer reflex, the reflex being more active when the pressure developed by expiration is increased, depressed when the expiratory pressure is decreased.

Moyer and McKettrick (91) have observed that it may be unwise to use pentothal alone for anesthesia to permit surgical pneumothorax, in as much as the exaggeration of the Hering-Breuer reflex, combined with a tendency to develop "expiratory dominance" during the slight to marked asphyxia that accompanies surgical pneumothorax without assisted or controlled respiration, may set the stage for a fatal expiratory apnea when the lung is expanded to permit closure. A similar set of conditions leading to death in experimental animals during surgical pneumothorax never occurred under ether in their experience because of the inactivation of the reflex response to inflation of the lungs by this agent.

The depth of anesthesia, as judged by the depression of the response of the respiratory center to carbon dioxide excess and deficit, may be determined either by the duration of overventilation apnea or by the duration of reflex apnea which results from sustained inflation of the lung (78). Although true only with pentothal, avertin and morphine for the reasons already given, the deeper the narcosis, the more prolonged is the apnea caused by the Hering-Breuer reflex. Conversely, with agents like ether and cyclopropane which block the reflex, the respiratory rhythm may not interrupted by lung inflation during deep anesthesia.
We have considered the influence of anesthetic agents upon the Hering-Breuer reflex in some detail because of the variety of effects which result with different agents. Since we believe that it is generally desirable to assist the respiration during inhalation anesthesia, with certain exceptions, it is important to know that the “feel” of the patient as ascertained by pressure on the breathing bag, as well as by other muscular signs, is determined both by the anesthetic agent (as related to the Hering-Breuer reflex) and by the depth of anesthesia. The Hering-Breuer reflex itself may be utilized, when not inactivated, to facilitate the taking of roentgenograms of the chest, cholangiograms and pyelograms (see below). The reflex is probably responsible for the sensation imparted of active expiration during light ether and nitrous oxide anesthetics.

**The Bronchial Smooth Muscle (see table 2)**

Macklin (92) has listed most of the drugs that constrict or dilate the bronchi and bronchioles according to mode of action, whether on muscle, nerve or ganglions. Using excised human and animal lung tissue, Adriani and Ravenstine (79) observed constriction of varying degrees with nitrous oxide, ethylene, the barbiturates including evipal and pentothal, opiates, cyclopropane and paraaldehyde. Bronchial dilatation was noted with the ethers (diethyl, divinyl, ethylpropyl, cyclopropylmethyl), chloroform, ethyl chloride, tribromethanol, amylene hydrate and trichlorehanol. These results are thought to be due to various combinations of stimulation or depression of parasympathetic ganglions or nerves, sympathetic nerve endings or the bronchial and bronchiolar smooth muscle. Curare (d-tubocurarine chloride, curarine hydrochloride and intoctrocin) has a bronchoconstrictor action in animals which is the result of the liberation of histamine from the tissues by the action of curare; the bronchoconstriction may be prevented or reversed by antihistamine drugs (93, 94).

These effects, which may help or hinder pulmonary ventilation, have been seen during clinical anesthesia, and may determine the choice of anesthetic agent for patients with diseases of the lungs. The use of agents that tend to cause bronchoconstriction may constitute an indication for manual assistance to respiration. Difficulties in ventilation when encountered during the anesthesia, as indicated by an increased resistance to bag pressure when the airway is clear, may dictate a change in the agent or the use of a remedial agent or technic.

**The Circulatory System**

The cardiovascular system in general is more resistant than the respiratory system to oxygen lack, carbon dioxide excess and narcotic drug action. The failure of respiration during inhalation anesthesia prevents further absorption of the anesthetic, thus protecting the
circulation; the failure of respiration from oxygen lack or from intravenous anesthesia generally occurs before the failure of cardiac action, and allows time for resuscitation provided the heart continues to beat. Opponents of the technic of controlled respiration argue that accidental respiratory failure from anesthetic overdosage precludes circulatory failure, whereas deliberate apnea during the technic may lead to accidental and irreversible circulatory failure. Arguments will be given to show why circulatory failure from anesthetic overdosage need not occur.

**Summary of Physiologic and Pharmacologic Factors**

This discussion is given to emphasize factors that tend to lead to the accumulation of carbon dioxide during anesthesia, possibly to narcotic or depressant levels. They are as follows:

1. Many surgical positions. 2. The closed method of administering anesthetic gases. 3. The greater diffusibility of oxygen as compared with carbon dioxide. 4. The tendency to use oxygen-rich mixtures. 5. The pharmacologic effects of anesthetic agents on the respiratory center, the chemoreceptor reflexes, and the bronchi and bronchioles.

Because this tendency may be best corrected by manual assistance to respiration, which in turn may impose altered respiratory pressures and varying degrees of hyperventilation, the relationships of respiration, circulation and pulmonary lymph flow are considered; the effects of respiratory acidosis and alkalosis are also discussed. The Hering-Breuer reflex, from the physiologic standpoint, is considered at some length in relation to newer information, because of its obvious dependence upon positive intrapulmonary pressures and because its activity may be used as an index to the depth of anesthesia.

The use of intermittent positive pressure for assisting or controlling respiration also may overcome the tendency to development of atelectasis that results from many surgical positions or from the uniform, machine-like respiration that characterizes surgical anesthesia.

*(To be Continued in the November 1950 Issue)*

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