# IS BREATHING FUNDAMENTALLY A REFLEX PHENOME-NON?[1] By ROBERT GESELL and CARL MOYER, Department of Physiology, University of Michigan, Ann Arbor, Michigan.

IT has been long assumed, but it is still uncertain, that the so-called respiratory centre possesses independent automaticity. On the other hand, there is abundant evidence of the importance of reflex control of respiratory movements. Whether the rhythmic discharge of the respiratory centre will eventually prove to be a localised physico-chemical process [Gesell, 1925] in and about a group of neurones on the motor side of the respiratory neurone chain which is modified by afferent nerve impulses, or whether it will prove to be fundamentally a reflex phenomenon [Schaffer, 1932; Gesell and Moyer, 1935] modified by chemical conditions along the respiratory reflex arcs, is the primary question raised by the present paper.

The adjustment of pulmonary ventilation by chemical stimulation of sensory nerve fibres ending in the carotid gland, demonstrated by Heymans [1927], and now abundantly confirmed, gives emphasis to the reflex mechanism of control. The stimulation by carbon dioxide after sinus denervation and double vagotomy [Heymans, 1927], the effects of arterial injection ($Na_2Co_3$, $NaHCO_3$, $NaCN$, and $Na_2S$) beyond the carotid gland [Owen and Gesell, 1931; Winder, Winder and Gesell, 1933; Winder and Winder, 1933], and the stimulation of respiration from painting the floor of the fourth ventricle with $NaCN$ and $Na_2S$. Owen and Gesell [1931], however, force us to give due consideration to the possibility of a direct chemical action on the respiratory centre itself. But until we have a more complete explanation of these effects the question of direct central chemical action versus reflex chemical stimulation will remain unanswered for reflex endings susceptible to chemical stimulation, quite obviously may exist within the brain itself. If such endings do exist, but for the time cannot be demonstrated, the solution of the control of respiration will be difficult indeed. The situation will be comparable to that existing before the opportune discovery of the rôle of the carotid gland by Heymans.

Several years ago, when we were looking for new leads on the

mechanism of respiratory control, Drs. Glazer, Winkler, and Gay studied the effects of chemical changes on the response of the serratus anticus to reflex stimulation, to motor nerve stimulation, and to direct stimulation of the muscle itself.   The effects of mechanical asphyxia on the response to rhythmic submaximal reflex stimulation were variable [Glazer, 1929]. Most animals showed a decreased muscular response.   In a considerable number there was no decrease, but, on the contrary, contractions increased until the animal was allowed to breathe again.   Breathing carbon dioxide diminished the reflex response, intravenous injection of sodium carbonate and sodium cyanide increased the reflex response.

The variable results of mechanical asphyxia indicated the interaction of two opposing factors—reduction of reflexes from effects of acid accumulation and augmentation of reflexes from impaired oxidations.   Such deductions were supported by the results of Sherrington [1910] and of Brown [1909], who found that a certain degree of asphyxiation favoured the elicitation of reflexes.   Kaya and Starling [1909–10] stated that the increase in reflexes is due to a decrease in oxygen and not to an increase in carbon dioxide, and Lennox and Cobb [1928] found in epileptic individuals that attacks could be induced by breathing gaseous mixtures with low oxygen content, and that they are stopped by administration of high carbon dioxide mixtures.

Winkler [1929, 1930] found, in his hemorrhage experiments, that 87 per cent. of the hemorrhages increased the reflex response of muscle and 74 per cent. of the reinjections decreased the response.   In his low oxygen studies, lowered alveolar oxygen invariably increased the response.   Gay [1930 and 1931] elicited increased reflexes when low oxygen mixtures were administered by uniform artificial ventilation. The increased response could, therefore, not be due to an excessive blowing off of carbon dioxide which occurs during normal hyperpnea from anoxemia.   During uniform artificial ventilation with low oxygen mixtures the tissues are believed to turn more acid [Gesell, Krueger, Nicholson, Brassfield, and Pelecovich, 1932].   Gay, therefore, concluded that impaired oxidations may augment reflexes despite simultaneously increasing acidity.

By various procedures, data were obtained by Glazer, Winkler, and Gay indicating that the changes in amplitude of the reflexes were due primarily to changes in excitability of the synapses in the cord.   The changes in excitability of nerve and muscle were relatively smaller.

Comparison of reflex response and respiratory movements during lowered alveolar oxygen, cyanide injection, and hemorrhage and reinjection showed a decided parallelism.   This parallelism vanishes when we note the development of apnea and increased reflexes with intravenous injection of sodium carbonate and the increased ventilation and inhibition of reflexes from the administration of carbon dioxide.   Direct comparison of simple muscle reflexes and accompanying changes in

ventilation, therefore, leave us without pertinent information on the control of respiration through modification of existing respiratory reflexes.

This information was next sought by a more direct study of the influence of chemical conditions of the body on respiratory reflexes themselves. We have recorded the changes in breathing produced by faradic stimulation of cutaneous sensory nerves, the vagus and superior laryngeal nerve. Having established a fairly uniform response in a series of excitations of proper strength and duration, separated by adequate intervals of time, chemical changes were introduced which are known to modify pulmonary ventilation and to change the acid-base equilibrium and the rate of oxidations in the tissues, and the nerves were again stimulated. These chemical changes were accomplished by administration of gaseous mixtures of low oxygen content and of combined high oxygen and high carbon dioxide content, and by the injection of sodium cyanide, sodium carbonate, and sodium bicarbonate. In all of our records respiratory movements are recorded as changes in torso circumference by methods previously described, and ventilation was recorded with a Hutchinson spirometer.

The effects of changing the acid-base equilibrium on the response to faradic stimulation of the saphenous nerve are illustrated in fig. 1. In record 1, while the dog was breathing a high oxygen mixture, the saphenous nerve was stimulated for a period of 15 seconds with the coil at 3. At B the strength of stimulation was increased (C4), with a resulting increase in rate of breathing and the appearance of several short aborted inspirations. The second stimulation with the coil at 4 gave practically the same result, with an increase in rate from 15 to 53·3 respirations per minute. The drum was then stopped at D and carbon dioxide administered during the usual period intervening between stimulations. When the drum is restarted the increase in depth of respiration is readily seen. Stimulation at E now produced only a minor acceleration in rate from 16·9 to 23·3 respirations per minute, and the aborted inspirations were missing. The drum was stopped again at F and a $CO_2$ free high oxygen mixture was readministered. Early in this period of recovery the saphenous stimulation produced only a slightly greater acceleration, but later, at G, gross acceleration had returned again.

Blowing off carbon dioxide by artificial ventilation markedly changes the respiratory response to stimulation of the saphenous nerve, as might be expected from the foregoing results and as is clearly shown in record 2, fig. 1. In this record there are two responses to uniform faradic stimulation after equal periods of artificial ventilation shown at B and E and two responses after equal periods of normal ventilation C and F which follow on these periods of artificial ventilation. The irregularity of the record during artificial ventilation is simply an expression of
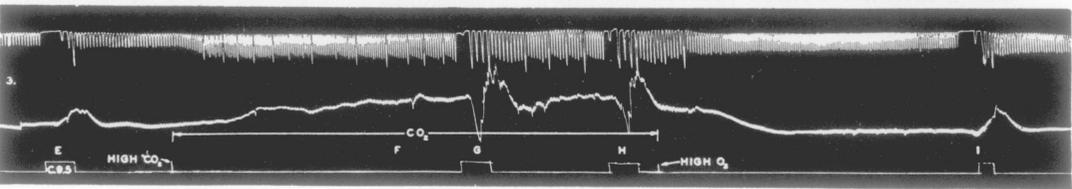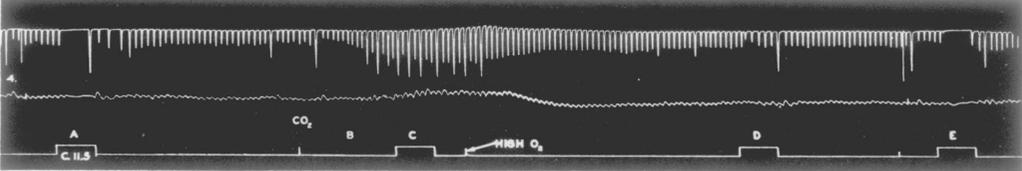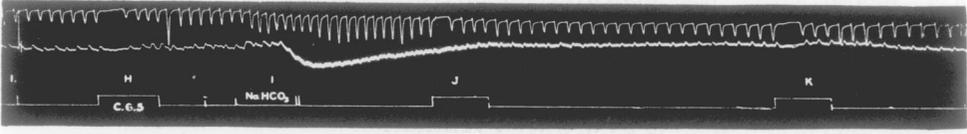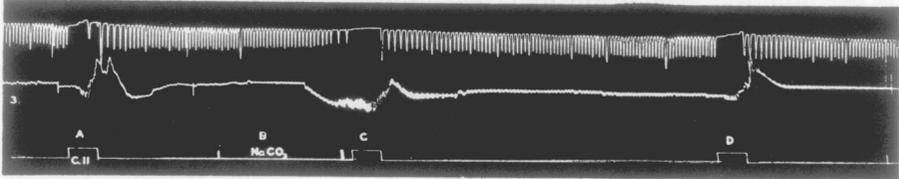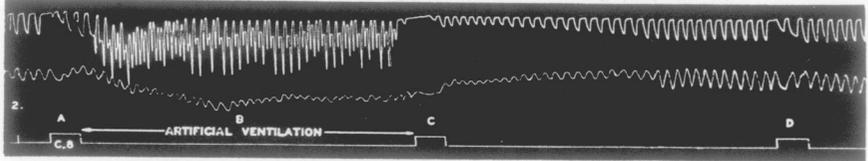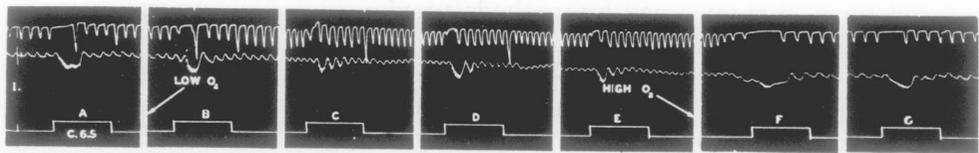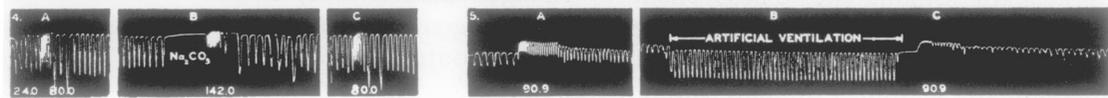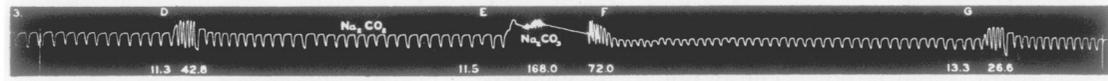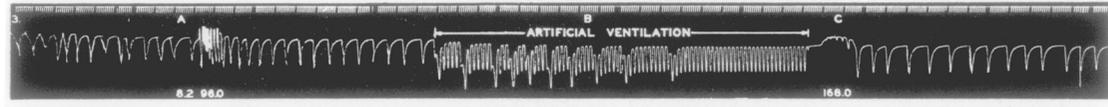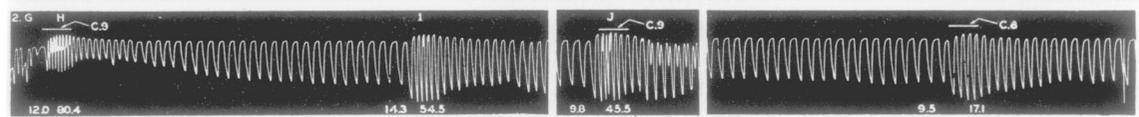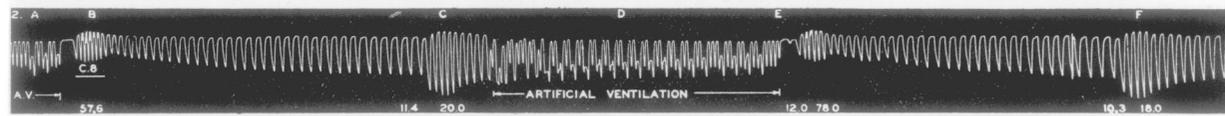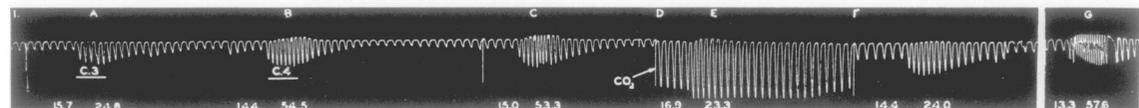
synchronised and lack of synchronised response of the animal to the action of the pump. Beginning at C, where breathing has about returned to normal from reaccumulation of carbon dioxide, the effects of stimulation are small. The rate increased from 11·4 to 20 respirations per minute, and the aborted respirations were missing. At E, following artificial ventilation, which is seen to be effective by the initial small breath just before stimulation, the effects of saphenous stimulation are markedly augmented. The rate increases from 12 to 78 respirations per minute and the aborted respirations are present. The same effects of hyperventilation and reaccumulation of carbon dioxide are seen with stronger stimulation with the coil at 9 in records 2H and I. The stronger stimulation increases the aborted inspirations so that now at H, following a period of artificial ventilation, the respiration rate has been increased to 80·4 as compared with 57·6 at 2B. Reaccumulation of carbon dioxide, to be sure, suppresses reflex augmentation at 2I, but not sufficiently to eliminate the aborted inspirations. The effects of change in strength of stimulation following consecutively under uniform conditions, after reaccumulation of carbon dioxide during normal breathing, are shown in observations 2J and K. The results from carbon dioxide depletion, therefore, complement those on carbon dioxide administration, indicating that a reduction of carbonic acid from either a normal or supernormal level is comparable in effects to increasing the strength of stimulation. Our results, therefore, agree with the conclusions of Glazer, Winkler, and Gay that reflex excitability is increased by a reduction in alveolar carbon dioxide pressure or hydrogen ion concentration of the body.

It appears that, in general, the lower the alveolar carbon dioxide pressures resulting from changing ventilation the smaller the respiratory excursions become during stimulation of the saphenous nerve. An extreme example of this is shown in record 3. When stimulation occurs during normal ventilation 3A, the excursions are fairly large and rapid. The rate increases from 8·2 to 96 per minute. At the close of the following period of artificial ventilation while the animal is apneic the saphenous nerve is stimulated. There is an appreciable decrease in the torso circumference. Respiratory excursions, at first sight, seem to be entirely missing, but if the record is carefully analysed small irregularities are apparent, indicating that respiratory movements are occurring at a rate not less than 168 respirations per minute. Within a few seconds following the end of stimulation the amplitude and rate return to normal. In record 5 the effects of over-ventilation seem limited to a

---

FIG. 1.—Effects of $CO_2$, forced ventilation, and $Na_2CO_3$ on the respiratory response to stimulation of the saphenous nerve.

FIG. 2.—Effects of anoxemia, forced ventilation, $Na_2CO_3$, $NaHCO_3$, and $CO_2$ on reflex inhibition produced by stimulation of the superior laryngeal nerve.

reduction in amplitude alone. The rate before and after over-ventilation during stimulation are the same. This is an exceptional finding.

It might be concluded that the effects of over-ventilation are largely a summation of powerful rhythmic stretching and contraction of the vagal nerve-endings in the lungs; but if intravenous injections of sodium carbonate are substituted for over-ventilation the results are the same (see record 4, fig. 1). At 4A saphenous nerve stimulation increases the rate from 24 to 80 respirations per minute. Sodium carbonate is now injected and produces a prolonged apnea. Saphenous stimulation during this profound apnea suddenly initiates short rapid respirations occurring at a rate of 142 respirations per minute. A few minutes later at C the results of 4A are duplicated.

The superior laryngeal nerve which uniformly gives inhibition of respiratory movements with faradic stimulation was also studied under varying conditions. Examples of modified responses are illustrated in fig. 2. In record 2 the superior laryngeal nerve is stimulated at regular intervals, once at A during normal breathing, once at C immediately following a period of over-ventilation, and finally at D several minutes later. Increased inhibition immediately after over-ventilation is the invariable result. Intravenous injection of sodium carbonate produces the same prolongation of inhibition. Compare the responses at 3C with 3A and D. Breathing carbon dioxide mixtures invariably decreases the inhibitory effects of stimulation. Compare the results at 4C with those at 4A, D, and E. Note how slowly the reflex inhibition recovers from carbon dioxide saturation. Several minutes after readministration of high oxygen at D the inhibition is very slight, but at E it is well established again.

Intravenous injection of sodium bicarbonate which presumably increases ventilation by virtue of its $CO_2$ effect [Gesell, 1925] reduces the duration of reflex inhibition despite the decrease in hydrogen ion concentration of the blood. Compare the response to stimulation of the superior laryngeal nerve at 1J with that at 1H and 1K.

The effects of acid-base changes on the response to faradic stimulation of the central end of the cervical vagus nerve have a double interest, for graded stimulation under normal conditions produces a series of changing results. Weak stimulation produces a complete inhibition, becoming less and less as the strength of current increases and going into a definite acceleration. With further increase in current, acceleration finally gives way to complete inhibition. When a stimulus is selected which gives inhibition, carbon dioxide saturation and intravenous injection of sodium bicarbonate reduce or even abolish this reflex (see fig. 3, records 1, 2, and 3). After intravenous injection of sodium carbonate or after carbon dioxide desaturation from over-ventilation the reflex is increased; see observations 3E, G, and H, and 3J, L, and M of fig. 3.

When the reflex effect of stimulation of the cervical vagus is accelera-
tion, as it is in record 3, fig. 4, the administration of carbon dioxide
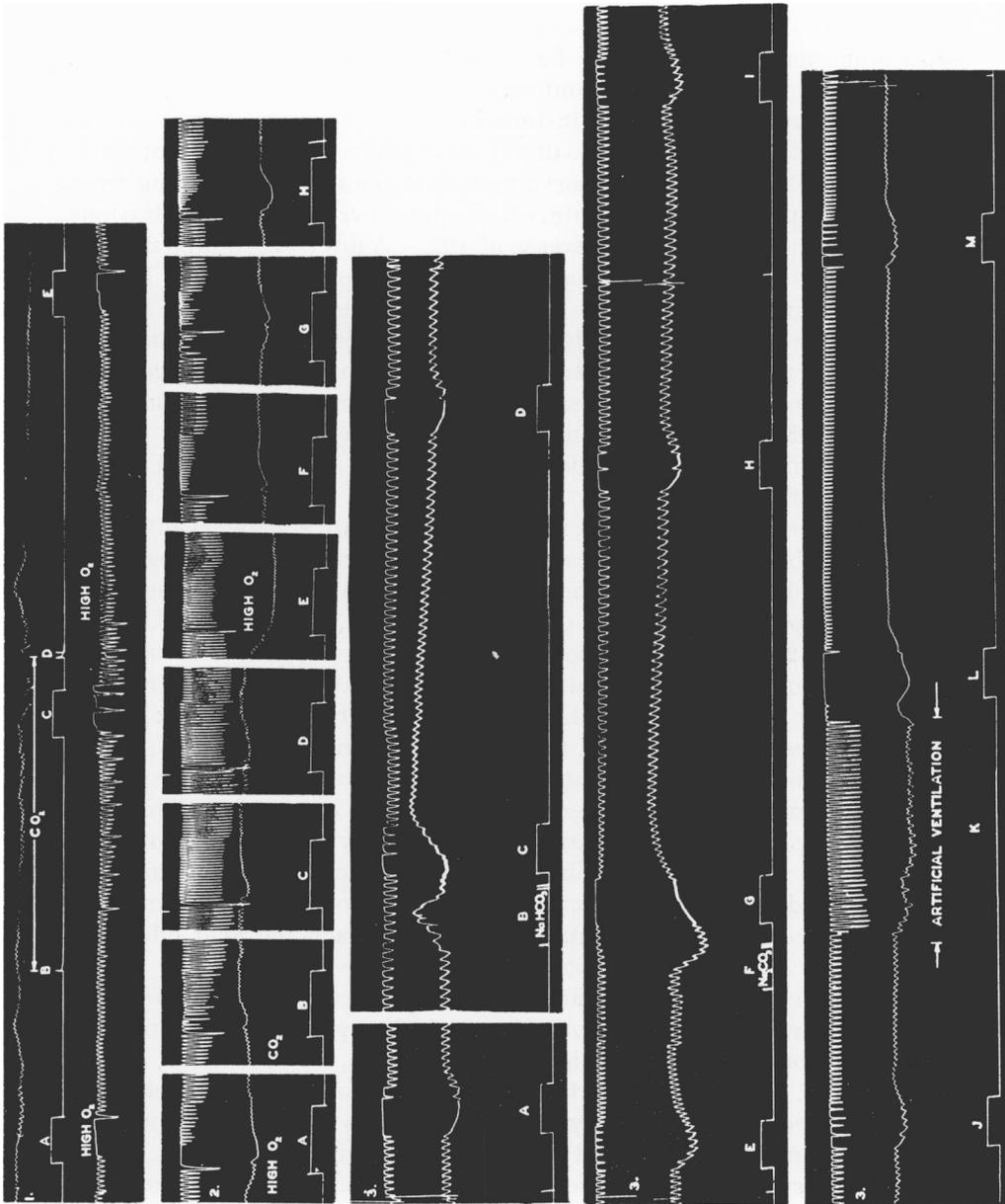


Fig. 3.—Effects of $CO_2$, $NaHCO_3$, $Na_2CO_3$, and forced ventilation on reflex inhibition produced by stimulation of the cervical vagus nerve.

reduced this reflex. At 3A, when the animal is breathing a high oxygen
mixture, the respiratory rate increases on vagus stimulation from 16·2
to 57 respirations per minute, an absolute increase of 40·8 respirations

per minute and a percentage increase of 252. At the height of the $CO_2$ effect at D the rate increases from 18 to only 36 respirations per minute, an absolute increase of 18 and a percentage increase of 100.

Typical effects of anoxemia on the response to stimulation of the saphenous nerve are shown in fig. 4, records 1G, H, I, J, and K, and 2E, F, G, and H, and may be compared with the effects of carbon dioxide saturation already considered in immediately preceding records on the same animal. At 1G, while the dog is breathing a high oxygen mixture, stimulation of the saphenous nerve increased the rate of breathing from 18·5 to 54 respirations per minute, an absolute increase of 35 respirations per minute and a percentage increase of 192. A low oxygen mixture was administered at 1H, and during the resulting hyperpnea the saphenous nerve was stimulated again at I. Respirations increased from 22·7 to 71 per minute, which is an absolute increase of 48 or a percentage increase of 213. Several minutes after readministration of high oxygen the absolute increase fell to 29·9 respirations per minute and the percentage increase to 182. Identical stimulation of the saphenous nerve during carbon dioxide saturation produced the effects already noted of reduction of reflex acceleration.

In records 2E, F, G, and H, fig. 4, the results are somewhat different. Both the absolute and percentage acceleration of breathing from stimulation of the saphenous nerve at F during anoxemia are less than during the preceding period of oxygen plenty, 2E, fig. 4. During recovery at 2G, when oxidations are above normal, the absolute and percentage increase in breathing is less than at 2F. Augmentation of saphenous acceleration is, therefore, not uniformly obtained; but so far as our observations go, and that is apparent in records 2A, B, C, and D, fig. 4, carbon dioxide saturation reduces the acceleratory reflex more than does comparable increased breathing from anoxemia. This lack of uniformity of the effects of anoxemia is possibly attributable to a dual effect on the acceleratory respiratory reflex-augmentation by impaired oxidation and inhibition by increased hydrogen ion concentration if the augmented ventilation is insufficient to counteract the acid effects of anoxemia.

The same comparison of effects of carbon dioxide saturation and of anoxemia have been made for the cervical vagus nerve where such stimulation produces acceleration (see records 3A, B, C, D, E, F, and G, and 3H, I, J, K, L, M, and N, fig. 4). Before anoxemia, vagus stimulation increased the respiratory rate from 12 to 44·4 per minute, an absolute increase of 32·4 and a percentage increase of 270. During the early part of anoxemia the percentage as well as absolute increase in rate from vagus stimulation is greater than that of the preceding period of oxygen plenty; but during the latter part, when the rate of breathing is faster, only the absolute increase in rate exceeds that of the period of oxygen plenty. During the subsequent period of excessive
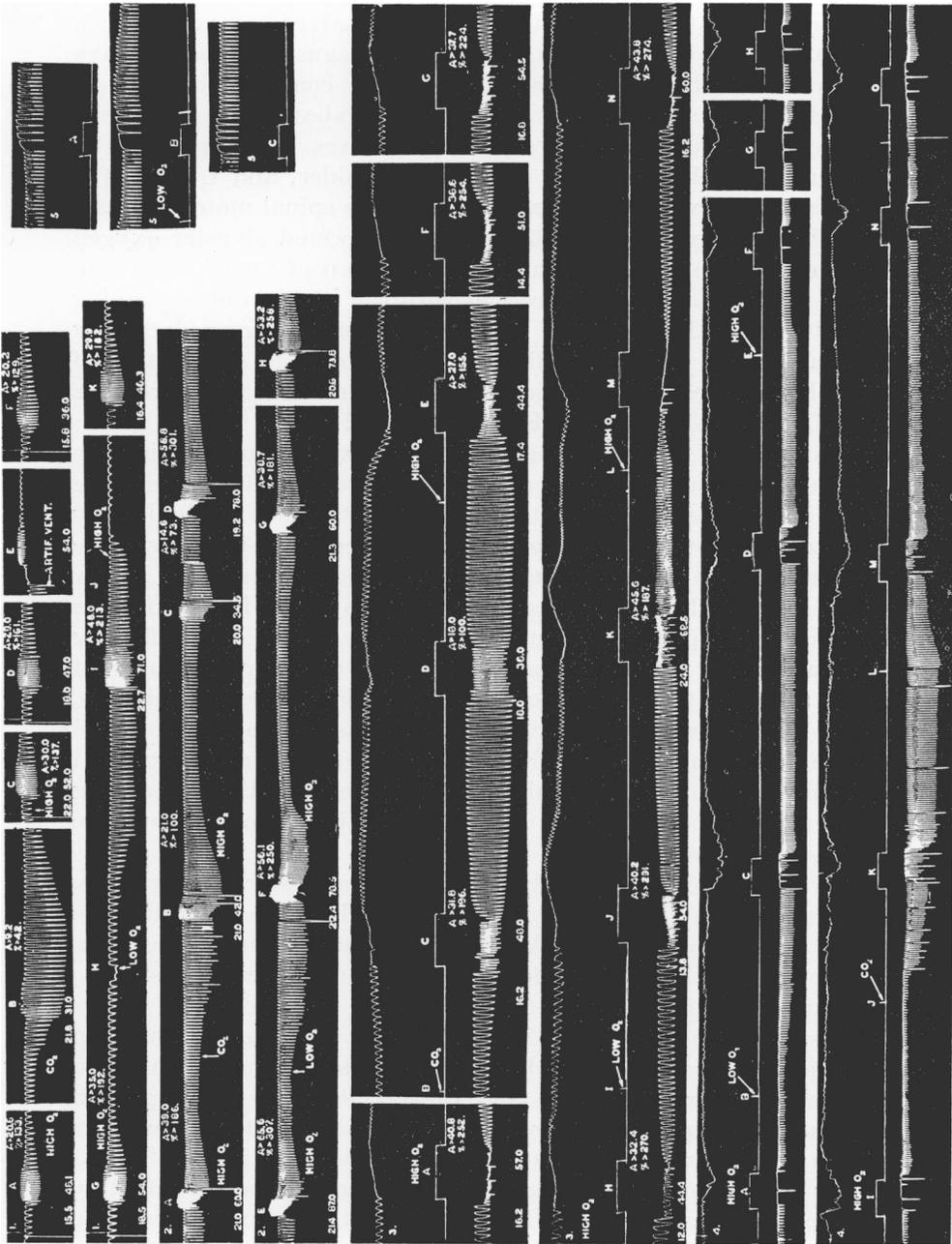
FIG. 4.—Records 1 and 2: Comparison of effects of anoxemia and of $CO_2$ saturation on the reflex response to stimulation of the saphenous nerve. Record 3: Comparison of effects of $CO_2$ saturation and anoxemia on the acceleration of breathing produced by stimulation of the cervical vagus nerve. Record 4: Comparison of effects of anoxemia and $CO_2$ saturation on reflex inhibition of respiratory movements produced by stimulation of the cervical vagus nerve. Record 5: Effects of anoxemia on reflex inhibition of respiratory movements produced by stimulation of the cervical vagus nerve after double vagotony and double sinus denervation.

oxidations with re-establishment of oxygen plenty, stimulation of the vagus nerve produces only a few respirations, and towards the close of the period of stimulation the animal is apneic. Later in recovery, when hyperoxidations have subsided, the effects of vagus stimulation have again increased. The effects stand in striking contrast to those of carbon dioxide shown in the record immediately above.

Our findings on acceleratory respiratory reflexes, therefore, seem to be in general accord with those of Glazer, Winkler, and Gay on the effects of carbon dioxide and anoxemia on simple spinal motor reflexes.

When, however, we compare the effects of lowered alveolar oxygen and carbon dioxide saturation on reflex inhibition of breathing we no longer find opposite effects and are met with the problem of explaining an invariable reduction of reflex inhibition of breathing produced by anoxemia as well as by carbon dioxide saturation with stimulation of the cervical vagus nerve or superior laryngeal nerve (see fig. 4, records 4A, B, C, D, E, F, G, and 4I, J, K, L, M, N, and O).

Since anoxemia adds an augmenting reflex component through stimulation of the carotid gland, and of the vagal chemically sensitive endings and of the respiratory centre, the augmentation of the inhibitory effect of vagal stimulation, if such actually occurs, might easily be masked and require special methods for its demonstration. A few experiments were, therefore, tried in which the vagal inhibition was studied after sinus denervation and during vagal block. The difficulty of such experiments is that animals so prepared are very unstable and respiration is likely to fail during anoxemia. Some few experiments, however, were performed in which breathing was not so affected, and in these animals stimulation of the central end of the vagus produced greater inhibition during anoxemia (see fig. 4, record 5B) than during oxygen plenty in records 5A and 5C. Such findings, though few, were repeatable in single animals.

We have, therefore, tentatively concluded that respiratory reflexes, inhibitory as well as excitatory, may be diminished by carbon dioxide saturation and increased by carbon dioxide depletion and anoxemia. We are employing these conclusions in a preliminary way to analyse various respiratory phenomena.

The first of these phenomena is the relation of pulmonary inflation to pulmonary ventilation. The literature dealing with the inhibition of breathing from lung inflation and the acceleration resulting from collapse has been repeatedly summarised and will not be reviewed in our present discussion. The question whether the effect is one of intra-pulmonary pressure or one of lung volume has recently been studied by Hammouda and Wilson [1932]. Having varied the volume of the lung by changing the pressures outside the thoracic cage and maintaining intrapulmonary pressure constant, they ascribed changes in pulmonary ventilation to changes in lung volume.

To further test the views on the nature of the mechanical stimulus producing changes in respiratory rhythm we have preferred to alter
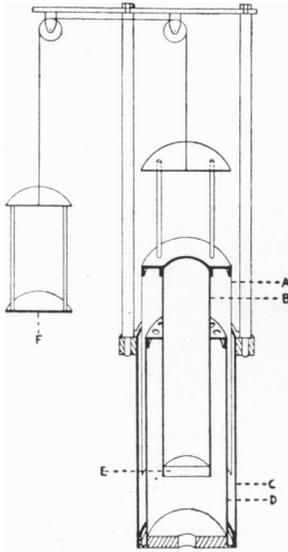
Fig. 5.—Steel mercury spirometer used for studying effects of graded positive and negative intrapulmonary pressures. A, Wall of steel spirometer. B, Inner cylinder for receiving weights supported at E. C and D, Concentric steel tubes. The space between these tubes contains the mercury on which the spirometer is floated. F, Pan for counterweighting to produce negative intrapulmonary pressures.

the intrapulmonary pressures as well as the pulmonary volumes. By connecting the trachea with a rebreathing tank provided with a specially
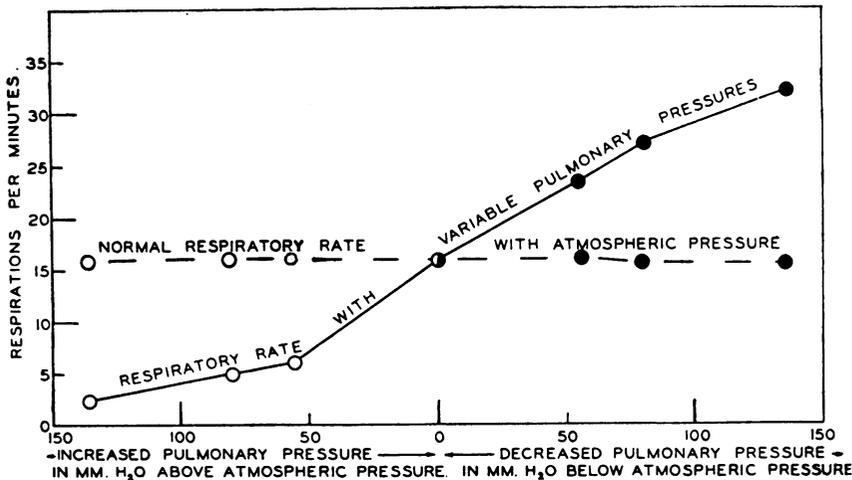
Fig. 6.—Graph relating rate of respiratory movements to positive and negative intrapulmonary pressures.

constructed Hutchinson spirometer floating in a mercury bath (see fig. 5) we were able to modify the filling of the lungs by weighting and counterweighting of the spirometer. By placing weights within the

inner cylinder of the floating bell, positive pressures were conveniently graded.   By counterweighting the bell, negative pressures were graded.

Results of a series of negative and positive pressures with the control rate at barometric pressure for each observation are shown in fig. 6. Within certain limits it will be seen that breathing was roughly proportional to the intrapulmonary pressures.

Fig. 7, however, shows that the changes in rate of breathing are not a direct result of lateral pressure acting on pressure corpuscles in the
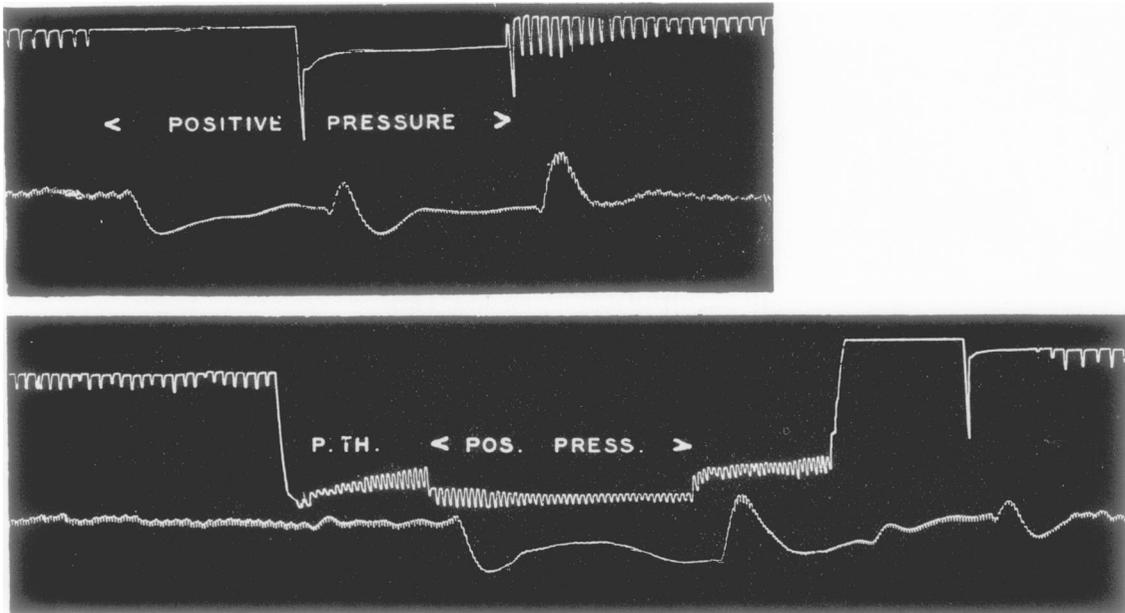


FIG. 7.—Records showing that pulmonary volume rather than intrapulmonary pressure determines respiration rate.  Upper record shows marked slowing of breathing produced by positive pressure under otherwise normal conditions. Lower record shows high rate of breathing after applying the same positive pressure during closed pneumothorax with the lungs partially collapsed.

walls of the pulmonary tubules and saccules, for the effect of any positive pressures seems to be dependent on the degree of filling of the lungs. For example, an increase in intrapulmonary pressure under otherwise normal conditions may produce a marked inhibition of rate (see upper record of fig. 7), but after admitting air within the pleural cavity permitting a partial collapse of the lungs the same increase in positive intrapulmonary pressure fails to slow the rate below normal (see lower record of fig. 7).   The rate of breathing falls from 72 to 66 per minute, which is still 26 breaths faster than normal.   Since the air cushion between the lungs and the thoracic walls opposes inflation of the lungs it must be concluded with Hammouda and Wilson [1932] that the major

deformation of the pulmonary sensory endings occurs primarily as a result of stretching of the lungs.

But the question which interests us particularly is whether the response to change in volume noted in fig. 6 is attributable to excitation of one set of pulmonary fibres which on stretching of the lungs produces inhibition, or whether the response, in agreement with the views of Hering and Breuer and others, might not be attributable to an additional set of fibres which is stimulated by a collapse of the lungs. With the introduction of electrical methods in the study of vagal function data have accumulated definitely indicating the presence of two such sets of vagal afferent fibres [Keller and Loeser, 1929, and Adrian, 1933], but the relative importance of these two sets of fibres in the functional control of ventilation requires further study.

Granting that carbon dioxide depletion augments respiratory reflexes and that carbon dioxide saturation has the opposite effects, we tentatively concluded that if the relation of respiratory rhythm to intrapulmonary pressure is primarily a function of a single reflex, namely, the inhibitory stretch reflex, then intravenous injection of carbonate, if it produces effects by augmentation of prevailing reflexes as well as by altering the degree of chemical excitation at the carotid gland and respiratory centre, might inhibit breathing at any pulmonary volume. Conversely, if carbon dioxide produces acceleration by inhibition of prevailing reflexes as well as by chemical excitation, and assuming the pulmonary stretch reflex is the controlling reflex, then carbon dioxide might accelerate breathing at any pulmonary volume. On the other hand, if there are two prevailing pulmonary reflexes—an inhibitory reflex which is predominant during any stretched condition of the lung above normal volume, and an acceleratory reflex which is predominant during any collapsed condition of the lung below normal volume—the carbonate injection might slow the breathing when the lungs are inflated, accelerate the breathing when the lungs are collapsed, and have no rate effect when the lungs are at natural volume. Carbon dioxide saturation by abolishing or reducing the inhibition resulting from a stretched condition of the lung might accelerate breathing and by abolishing an acceleratory reflex from a collapsed lung might slow the breathing.

The results of an experiment based on these assumptions are shown in fig. 8. The first strip of record shows a normal rate of 14 breaths per minute while breathing at atmospheric pressure. The second strip shows a slower rate of 10 breaths while the animal is breathing at a slightly positive pressure. A standard intravenous injection of carbonate now produces a temporary slowing to 4·5 breaths per minute. The animal is next returned to atmospheric pressure and the respiratory rate increases to 15·5 respirations per minute. Intravenous injection now produces little change in rate. The effect is primarily one of amplitude. A negative pressure is now established and the rate rises
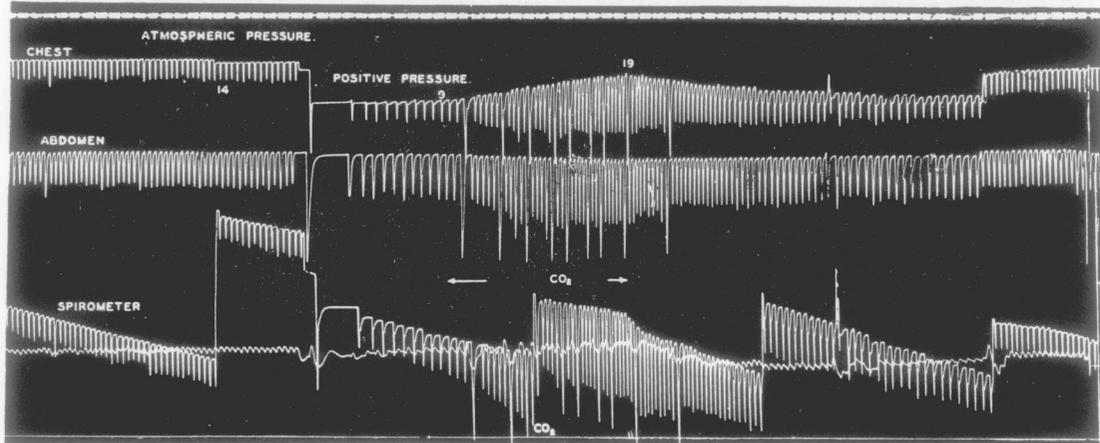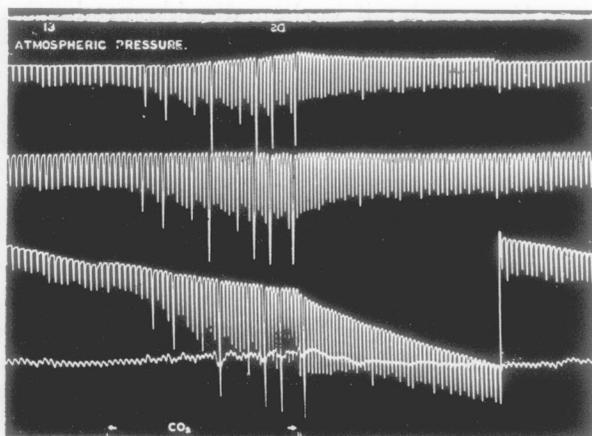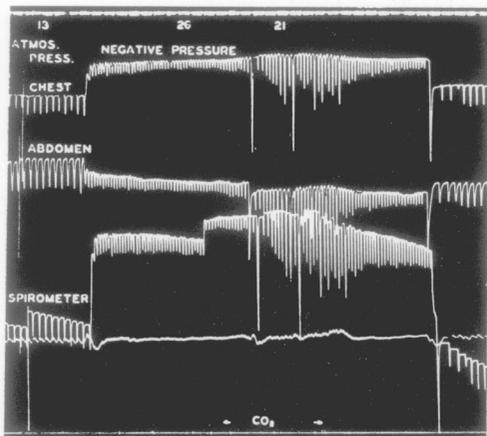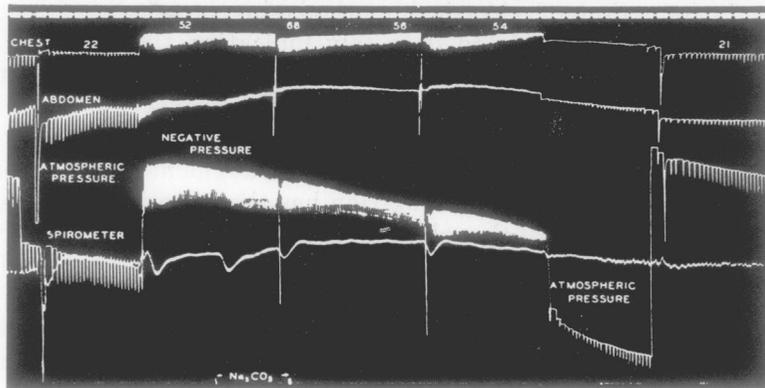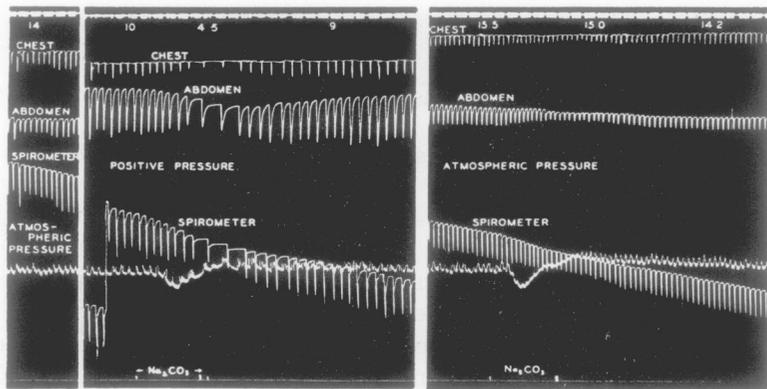
from 22 to 52 respirations per minute. During this period of negative intrapulmonary pressure carbonate injection increases the rate of breathing from 52 to 68.

The effects of carbon dioxide saturation at different lung volumes are illustrated in fig. 9. In the lower record, positive pressure was applied and the normal rate reduced from 14 to 9 per minute. During this positive pressure carbon dioxide increased the rate of breathing from 9 to 19 respirations per minute. In the upper right-hand record the dog is breathing at atmospheric pressure and the rate has returned to 13 respirations per minute. Carbon dioxide increased the rate to 20. In the upper left-hand record, negative intrapulmonary pressure was established and the rate of breathing increased from 13 to 26. Carbon dioxide now decreased the rate to 21. From these results it is inferred that lung volume is a factor determining the mode of response to chemical changes by changing the relative dominance of individual pulmonary reflexes.

Those who have had the opportunity of making many intravenous injections of sodium carbonate will probably recall great variations in effects. In many animals breathing under normal conditions at baro-metric pressure, carbonate may produce no appreciable slowing but a marked reduction in tidal air amounting almost to apnea. In others there is a reduction in rate as well as amplitude. It is, therefore, interesting to speculate whether or not the volume of the lungs differs sufficiently from dog to dog to alter the predominance of vagal reflexes which in turn determines the effects of carbonate. If such differences in chest volume occur, the causative factors producing them might prove to be profitable study not only from a theoretical point of view but for a practical application of the control of breathing during pathological disturbances and during surgical operations.

If our conclusions are correct concerning the augmentation of reflexes by carbon dioxide depletion, then the apneas which so commonly occur following augmented ventilation or intravenous injection of sodium carbonate can no longer be explained on the basis of depressed excitability of the respiratory centre. An explanation more acceptable to our present views would be that apnea is a result of increased excit-ability at a time when inhibitory reflexes are prevailing, for if excitatory impulses are made predominant during carbonate apnea breathing may

FIG. 8.—Records showing that pulmonary volume determines the type of respiratory response to intravenous injection of $Na_2CO_3$. The upper records show a marked slowing of the respiratory rhythm by $Na_2CO_3$ when the lungs are inflated. The lower record shows acceleration of respiratory rhythm by $Na_2CO_3$ when the lungs are partially deflated.

FIG. 9.—Records showing that pulmonary volume determines the type of response to administration of $CO_2$. The upper left-hand record shows a slowing of the respiratory rhythm by $CO_2$ when the lungs are partly deflated. The remaining two records show acceleration of the respiratory rhythm with the lungs normally inflated and super inflated.

become excessive. See, for example, record 4A, fig. 1, in which the saphenous nerve is stimulated with a resulting increase in rate of breathing from 24 to 80. Carbonate is now injected in record 4B, producing a prolonged apnea. During this apnea the saphenous nerve is stimulated again. The increase in breathing is more excessive. It increases from apnea to 142 respirations per minute. Obviously our views on carbonate apnea must be drastically revised.

Another question which needs further study concerns the interdependence of rate and amplitude of breathing. Are they closely interdependent as they seem to be when breathing increases in amplitude as the rate decreases from double vagotomy, or may they vary independently as they seem to when amplitude of breathing changes without an associated change in rate, as sometimes happens with carbonate injections? Both situations may probably prevail depending upon conditions. It is conceivable that a loss of vagal control or an augmentation of excitatory stimulation through the carotid gland are each alone sufficient to increase amplitude. We have shown that carotid gland stimulation when the vagus nerves are blocked may produce mainly an increase in amplitude, but when the vagus nerves are physiologically intact similar stimulation produces much greater acceleration [Gesell and Moyer, 1934], indicating the great interaction of sensory nerve impulses, and showing the dependence of vagal function on extra vagal afferent nerve impulses.

The relatively rapid rate of breathing of anoxemia as compared with that of carbon dioxide saturation is a related question. In accordance with the accelerating action of the vagus nerves as postulated by Hering and Breuer, any influence abolishing or reducing their function, whether by impairment of initiation of impulses at the vagal endings or impairment of conduction or effectiveness of the impulses at any point along the reflex arc, should exert a slowing effect. Theoretically, carbon dioxide may produce two effects—inhibition of respiration by depressing the vagal reflex arc, and excitation by direct action on the carotid gland and respiratory centre. If the excitatory component is weak and the inhibitory component is strong, slowing of the respiratory rhythm is likely to occur. Such results are not uncommon. If the accelerating component is relatively strong acceleration is likely to occur. The same factors are assumed to be working in hyperpnea of anoxemia, but in this instance the acceleratory function of the vagus nerves is thought to be augmented as well as the acceleratory reflex initiated at the carotid gland. By virtue of the weakening of two acceleratory reflexes by carbon dioxide and the strengthening of the same reflexes by anoxemia the relatively rapid rate of breathing during anoxemia as compared with that of carbon dioxide saturation is theoretically explained.

Supporting by analogy we recall that stimulation of the saphenous nerve, which compares with the chemically initiated excitations,

produces less acceleration during cold block of the vagus nerves than when the nerves are physiologically intact. A subintact vagal reflex arc occurring during carbon dioxide saturation plus peripheral chemical excitation should, therefore, produce less acceleration than super intact vagal arc occurring during anoxemia plus similar excitation. The greater acceleration from saphenous stimulation during anoxemia as compared with that during carbon dioxide saturation supports the argument.

In general, our present experiments point to an important control of breathing through reflex action. Although they indicate that breathing may be primarily a resultant of a large variety and large number of afferent nerve impulses arising in various parts of the body which resultant is influenced by chemical changes on all respiratory reflex arcs, there is at present no positive evidence that the respiratory centre does not possess independent automaticity, and inasmuch as the heart presents a pertinent analogy of control of an automatic rhythm through two sets of impinging nerve impulses such a possibility cannot be ignored. Be that as it may, our outlook on respiratory control for a time must be guarded. The fact that carbonate may slow or accelerate breathing depending on the intrapulmonary pressures obtaining and that the effects of carbon dioxide saturation may be reversed by controlling the size of the lungs modifies our views on chemical stimulation. But the tentative conclusions based on the present results are of such import that they should be accepted with reserve until they may be put to a longer and more vigorous test. Such a test may reveal some hidden and unexpected variable.

In the meantime, however, no harm can come from an attempted application of the underlying principles to the control of other systems. The well-recognised effects of carbon dioxide and of anoxemia on circulatory phenomena suggests the desirability of studying the influence of chemical changes on circulatory reflexes.

## Summary.

Whether the rhythmic discharge of the respiratory centre is a localised physico-chemical process modified by afferent impulses, or a reflex phenomena modified by chemical conditions, is considered.

Effects of varied combinations of afferent inflow suggest that breathing may be largely a resultant of numerous and various afferent nerve impulses.

The effectiveness of afferent impulses is profoundly influenced by chemical changes capable of modifying breathing. Results indicate depression of excitatory and inhibitory respiratory reflexes by $CO_2$ saturation and augmentation by $CO_2$ depletion and anoxemia. These findings are tentatively employed to analyse respiratory phenomena.

The indirect proportionality of rhythm to intrapulmonary pressure is a reflex effect of changing lung volume. Assuming only a single inhibitory vagal reflex, augmentation of this reflex by sodium carbonate could slow the rhythm and depression by $CO_2$ could accelerate it, at any pulmonary volume. Graded volume change with a dual vagal reflex control could at some point reverse the effects of both $CO_3$ and $CO_2$. Experimentally $CO_3$ retards breathing during inflation, accelerates during deflation and reduces amplitude at neutral volume. $CO_2$ acceleration during inflation is reversed to retardation during deflation. Lung volume, therefore, importantly determines the mode of response to chemical influences by changing the relative dominance of individual pulmonary reflexes.

Carbonate apnea is not due to lost excitability, but most probably to augmentation of vagal inhibitory reflexes and possibly other stretch reflexes, for saphenous stimulation during apnea produces super-excessive breathing.

Carbon dioxide administrations under otherwise normal conditions may produce its relatively slow breathing by depressing the vagal accelerating function by chemical vagotomy. Anoxemia may produce its relatively rapid breathing by augmenting this function.

The present experiments indicate the great importance of reflexes and their modification through chemical changes and suggest the breathing may be fundamentally a reflex phenomena. On the other hand, they are not necessarily opposed to an automatically discharging centre under the influence of chemical and afferent nerve impulse changes.

It is suggested that the influence of chemical changes on circulatory reflexes may be a factor in the control of circulation.

REFERENCES.

ADRIAN, E. D. (1933). *J. Physiol.* **79,** 332.
BROWN, T. G. (1909). *Quart. J. Exp. Physiol.* **2,** 243.
GAY, H. (1930). *Amer. J. Physiol.* **95,** 519.
GAY, H. (1931). *Ibid.* **98,** 60.
GESELL, R. (1925). *Physiol. Rev.* **5,** 551.
GESELL, R., KRUEGER, H., NICHOLSON, H., BRASSFIELD, C., and PELECOVICH, M. (1932). *Amer. J. Physiol.* **100,** 202.
GESELL, R., and MOYER, C. (1935 *a* and *b*). *Quart. J. Exp. Physiol.* **24,** 315, 331.
HAMMOUDA, M., and WILSON, W. H. (1932). *J. Physiol.* **74,** 81.
HEYMANS, J. F., and HEYMANS, C. (1927). *Arch. Int. Pharmocodyn.* **33,** 273.
KAYA, R., and STARLING, E. H. (1909–10). *J. Physiol.* **39,** 346.
KELLER, C. J., and LOESER, A. (1929). *Ztschr. Biol.* **89,** 373.
LENNOX, W. G., and COBB, S. (1928). *Medicine,* **7,** 105.

OWEN, H., and GESELL, R. (1931).   *Proc. Soc. Exp. Biol. N.Y.* **28,** 765.
SHARPEY-SCHAFER, E. (1932).   *J. Physiol.* **75,** 130.
SHERRINGTON, C. S. (1910).   *Quart. J. Exper. Physiol.* **3,** 213.
WINDER, C. V., and WINDER, H. O. (1933).   *Amer. J. Physiol.* **105,** 337.
WINDER, C. V., WINDER, H. O., and GESELL, R. (1933).   *Ibid.* **105,** 311.
WINKLER, A. (1929).   *Ibid.* **89,** 243.
WINKLER, A. (1930).   *Ibid.* **94,** 224.