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Hemorrhage and Ventilation.*

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Effects of hemorrhage and reinjection on the acidity of the arterial and venous blood were studied with the manganese dioxide, quinhydrone and hydrogen electrodes. Room air was administered by normal and artificial ventilation, by the closed circuit method. Pulmonary ventilation and changes in oxygen consumption were recorded.

Hemorrhage elicited an increased alkalinity of the arterial blood, and an increased acidity of the venous blood. The increased alkalinity of the arterial blood was greater than the increased acidity of the venous blood. Subsequent injection of the blood decreased the alkalinity of the arterial blood, and the acidity of the venous blood. The extent of these changes varied with the animal and with the amount of hemorrhage. The decrease in acidity of the venous blood on reinjection may be preceded by a temporary increase in acidity. The acidity may not return to normal. On reinjection, the arterial blood may turn more acid than normal, and fail to reach the normal acid value during recovery. The acidity changes occurring during hemorrhage were accompanied by decreased oxygen consumption and increased pulmonary ventilation, and re-injection was accompanied by reverse changes.

Granting an increased oxidation of hemoglobin during hemorrhage, the increased alkalinity of the arterial blood seems related to increased pulmonary ventilation, and an increased blowing off of carbon dioxide.

Hemorrhage during constant artificial ventilation elicited similar directional changes in acidity of the arterial and venous blood. These arterial changes in acidity might conceivably be explained by the improved ventilation, due to a decreased flow of blood through the lungs. This being true, the significance of volume-flow of blood through the respiratory center is supported. The increased alkalinity of the arterial blood during hemorrhage and normal ventilation would thus be a resultant of increased ventilation of the blood through increased pulmonary ventilation, and decreased volume-flow of blood.

The results of these experiments are in agreement with the com-

* With a note on an Electro-Chemical Working Hypothesis of Respiratory Control, by Robert Gesell.

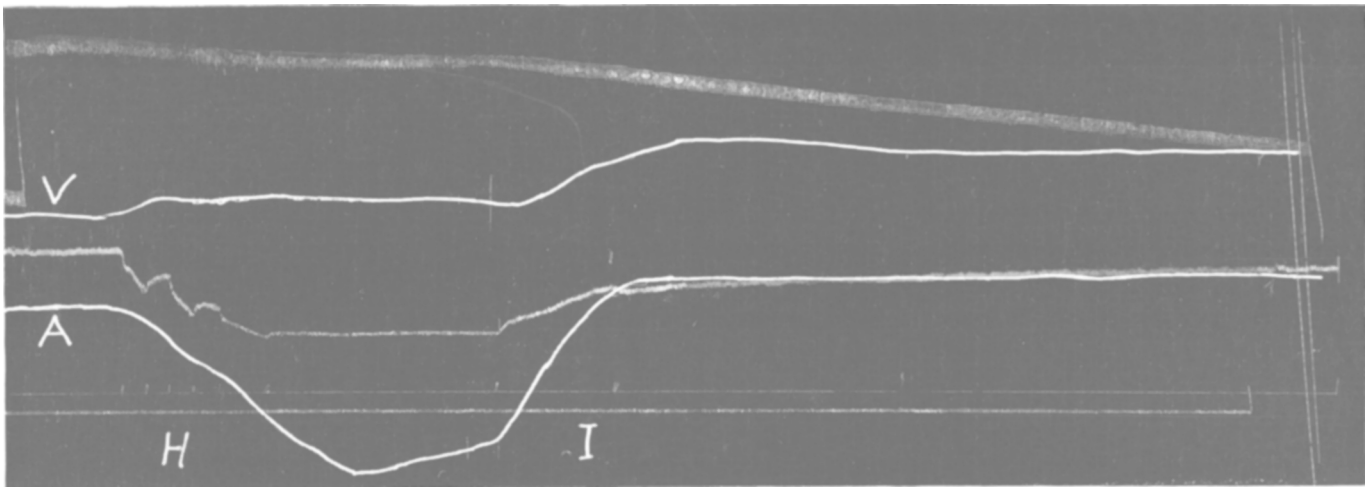

FIG. 1.

Record showing the effects of hemorrhage and reinjection on the acidity of the arterial and venous blood during normal breathing of room air. The acidity curves are marked A and V, respectively. Note the increase in pulmonary ventilation and decrease in oxygen consumption occurring with hemorrhage and the subsequent decrease in ventilation below normal on reinjection as the blood turns acid.

mon inverse relation between acidity of the arterial blood and respiratory movements. The relation between acidity of venous blood and pulmonary ventilation is more direct.

The decreased oxygen consumption during hemorrhage, and the excessive consumption following re-injection, suggest increased production and accumulation of acid in the respiratory center during hemorrhage. The failure of the venous blood to turn more acid than it does is probably related to the excessive ventilation of the arterial blood, both with respect to oxidation, and blowing off of carbon dioxide. The high oxidation of hemoglobin in the lungs should facilitate a correspondingly great reduction in the tissues.

The results here reported, as in the preceding two papers, support the view of the importance of acidity in the control of ventilation. But, similarly, they do not preclude the direct effects of lack of oxygen on oxidation.

Granting the possibility of this dual mechanism of control, the next step is to determine its probability.

If it be accepted that all biological phenomena are electrical phenomena, then all biological processes must be explained on a purely electrical basis. Whether or not the subject of respiratory control has advanced sufficiently to permit a formulation of a rational hypothesis based on electro-chemical changes might be questioned; but granting that excitation and conduction of excitation are electrical phenomena occurring with the aid of a membrane, and dependent on the composition of the fluids on each side of that membrane, an hypothesis is warranted if we can relate the behavior of the respiratory center to known changes occurring on both sides of the neurone membrane.

Heretofore, the difficulty of such approach consisted in the inability to associate consistently respiratory activity with any single variable or group of variables. It has been pointed out in preceding papers that increased pulmonary ventilation may occur in the presence of increased or decreased hydrogen ion concentration of the blood; with increased or decreased carbon dioxide tension of the blood; with increased or decreased oxygen tension of the blood. The accidental finding of the suppression of respiratory movements in volume-flow experiments by simple acceleration of the volume-flow of blood suggested the importance of a heretofore neglected factor, the metabolism of the respiratory center.

The behavior of the respiratory center on the administration of carbon dioxide and sodium carbonate was easily interpreted on the acid basis, but difficulty was encountered in harmonizing these effects with increased ventilation from intravenous injection of so-

dium bicarbonate. It was suggested that the "specific" action of sodium bicarbonate may be explainable on the basis of an actual increase in acidity of the interior of the cell due to the impermeability of the membrane to sodium bicarbonate and to the effect of sodium bicarbonate on the movement of acid. This was supported by *in vitro* experiments[1] and more recently by animal experiments.[2]

The increased pulmonary ventilation occurring with the administration of low oxygen, sodium cyanide, and in hemorrhage, was also contrary to the mechanism of acid control, for in all of these conditions hyperapnea is associated with increased alkalinity of the arterial blood. In these conditions the acid metabolism of the respiratory center, the coördination of the dual function of hemoglobin, and the transport of acid from the center, are factors controlling the acidity of the respiratory center. From the work of Hill[3] and Meyerhoff[4] on lactic acid, I concluded that though the amount of carbon dioxide formed as a result of decreased oxygen is diminished, this is more than balanced by an increased formation of lactic acid. Not only is the total production of acid increased within the cell, but the buffer is reduced as well. The increased ventilation could, therefore, be associated with increased acidity of the center. This increased respiration must of necessity lead to increased elimination of carbon dioxide. When oxygen is readministered the body is poor in carbon dioxide, and rich in sodium lactate, and since lactic acid is removed by returning in large part to the precursor state, avoiding oxidation, replenishment of oxygen should lead to a temporary increased alkalinity of the center. The early apnea of recovery from low oxygen is, therefore, also explainable on an acid basis.

Respiratory control seems intimately connected with changes in acidity and oxidation. A precise separation of these factors with the data at hand is exceedingly involved, for lowered oxygen transport to the center, means lowered acid transport from the center. Diminished oxygen supply to the center means not only reduced oxidations but increased acid formation as well. Beginning at the other end, increased acidity, let us say from the administration of carbon dioxide, presumably leads to lower oxidations, changes in acidity and changes in oxidation seem inseparable accompaniments, yet one of these factors might presumably be the dominating factor of respiratory control. Although I had called attention to findings of others, showing that respiration may be stimulated by the administration of carbon dioxide after low oxygen is ineffective, I was loathe to abandon the direct effects of low oxygen on oxidation.[5]

The electro-chemical hypothesis of respiratory control may assist in determining the relative effects of changes in acidity and oxidation, and is here offered as an assumption subject to test. Briefly put, the neurone membrane is a pulsatile oxidation-reduction system exhibiting rhythmic chemical and electrical changes subject to chemical and electrical influences which are determined by a combination of the metabolism of the nerve cell and by its immediate external environment.

This pulsatile mechanism has its counterpart in the behavior of the mercury peroxidate system studied by Bredig and Weinmayer,[6] and von Antropoff.[7] Pure mercury covered with a 10 per cent solution of hydrogen peroxide when brought to the proper alkalinity with sodium acetate and acetic acid exhibits a rhythmic formation and disappearance of a surface oxidation film. The behavior of the system is sensitive to changes in temperature and chemical and electrical influences resembling in many respects the behavior of biological rhythmic systems. Increased temperature, alkalinity and polarizing current may increase the rate of the rhythm and each rhythmic discharge is accompanied by a change in electrical potential. Granting Lillie's theory of conduction of excitation by self electrical stimulation, initiation as well as conduction may be accounted for by comparable electro-chemical mechanisms.

The behavior of the neurone membrane might then vary with its degree of oxidation, determined by the nature of the limiting fluids, and with the intensity of the self-generated current flowing through the membrane.

As a source of electrical energy in respiratory control I turned to the metabolism of the nerve cells and as a source of driving potential to the metabolic gradient of the nerve cell. Perhaps no living cell shows a steeper metabolic gradient rising from a level approaching zero in the neuraxone[8] to one approaching a physiological maximum in the nerve cell.[9] A high metabolism in the nerve cell proper is associated with a high production of hydrogen ions and a high rate of oxidation. Each of these factors represents a possible source of current.

The high production of acid, leading to an increased concentration of hydrogen ions within the cells leads to a polarization of the limiting membrane. Granting a greater acidity on the inside of the cell membrane the hydrogen ions concentrate at the outer surface of the membrane. The nerve cell becomes electrically positive. Current flows in the outer circuit from a region of high metabolic rate to a region of low metabolic rate and returns in the inner circuit from a region of low to a region of high metabolic rate. If

this reasoning be correct, other things remaining constant, the greater the acidity of the interior of the cell the greater the acidity potential gradient due to polarization, and the greater the polarizing current.

Assuming that the cell acts as an hydrogen electrode the effects are the same. The hydrogen ion concentration of the outer fluid remaining constant, the polarizing current will vary with the hydrogen ion concentration of the cell.

The difference in rate of oxidation at corresponding parts of the neurone, represented by the oxidation-reduction gradient, is the second source of current. Comparing the nerve cell to the Voltaic cell, the region of high oxidations would correspond to the zinc plate, and the region of low oxidations to the copper plate. Current should flow from the former to the latter in the internal circuit and in the reverse direction in the external circuit.

The oxidation and acidity currents are, therefore, opposite in direction. The resultant effect of the opposing currents may now be followed during depressed oxidations from the administration of low oxygen. Decreased oxidations lead to total increased acid production with an accompanying decrease in buffer. The acidity potential gradient current is increased. Decreased oxidation reduces the oxidation potential gradient and the current set up thereby. The resultant is an increased current in the stimulating direction.

A detailed discussion of various other points is reserved for a later paper. Suffice it to say that the hypothesis at present appears to meet the known facts in various forms of respiratory stimulation resulting from the administration of carbon dioxide, sodium bicarbonate, carbon monoxide, sodium cyanide, hemorrhage, etc.

A summary of experimental data on the relative effects of acidity and oxidation indicates the greater importance of the acidity factor in respiratory control. On the other hand, the hypothesis here presented seems to meet the known facts and support a broader interpretation, giving proportionate significance to acidity and oxidation. Whatever the conclusion, metabolism of the respiratory neurone appears to be the dominant factor controlling respiration.

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[1] Gesell, R., PROC. SOC. EXP. BIOL. AND MED., 1923, xx, 345.

[2] Gesell, R., and Hertzman, A. B., *Am. J. Physiol.*, 1926, lxxviii, 206.

[3] Hill, A. V., *Physiol. Rev.*, 1922, ii, 310.

[4] Meyerhof, O., *Arch. ges. Physiol.*, 1922, excv, 22.

[5] Gesell, R., *Physiol. Rev.*, 1925, v, 587.

[6] Bredig, G., and Weinmayer, *Z. Physik. Chem.*, 1923, xlii, 601.

[7] Von Antropoff, *Z. Physik. Chem.*, 1907, xlii, 513.

[8] Tashiro, S., *Am. J. Physiol.*, 1913, xxxii.

[9] McGintz, D. A., and Gesell, R., *Am. J. Physiol.*, 1925, lxxv, 70.