and about a dozen other elements whose spectra are of similar type.

In concluding let me remind you that many other aspects of dielectric constant deserve more study. There are the phenomena of electric double refraction and of the variation of dielectric constant with field strength which should open the way to a study of the law of force by which the electrical constituents of molecules are held together. There is the study of refractivity of particular electron groups and of chemical radicals, which can shed much light on the atomic arrangements in complicated molecules. There is the interesting question of the conditions of pressure and temperature at which the classical theory of dielectrics fails and a quantum theory must be employed—and of the nature of this quantum theory. There are innumerable problems of the effects of the strong local force fields of dipole molecules on such properties as heat of sublimation, association, dissociation, ionization, adsorption, conductivity, osmotic pressure, residual valency, electrical double layers, and so on. While all these have been pretty definitely related to deformability of molecules or to their electric doublet character, the field is an open one for research which will render more precise our understanding of this group of phenomena.

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ANOTHER OUTLOOK ON THE CHEMICAL REGULATION OF RESPIRATION[1]

THE regulation of respiration is a subject which is engaging the attention of physiologists, but the fluctuations of respiration in numerous pathological conditions have a significance which must likewise hold the interest of clinicians. I have, therefore, attempted to review a theory which seems at present to offer the most complete explanation of respiratory phenomena.

When respiration is suspended three outstanding changes in the arterial blood occur: an increase in the carbon dioxide tension; an increase in the hydrogen ion concentration and a decrease in the oxygen tension. When respiration is resumed the blood returns to its normal condition, and the conscious desire to breathe disappears. Such observations suggest that any one of these changes may be the factor controlling respiration, and several theories have been proposed explaining the chemical mechanism of respiratory control. According to one theory the respiratory center is stimulated by the free hydrogen ions of the arterial blood; according to another theory by a specific action of carbon dioxide, and according to another by a lack of oxygen in the arterial blood.

Several years ago my studies on the volume-flow of blood led me to doubt the prevailing theories of respiratory control, for I found that respiration could be stopped by simply accelerating unchanged blood through the respiratory center. Such experiments definitely indicate that the metabolism of the respiratory center itself and the volume-flow of blood through the center are important factors which must be considered in the ultimate explanation of the regulation of pulmonary ventilation. These conclusions are the result of a great number of diverse experiments devised to explain the harmful effects of hemorrhage and the beneficial effects of subsequent injection of non-nutrient solution.

In the submaxillary gland of the dog hemorrhage elicits a profound change in the volume-flow of blood. A 10 per cent. reduction of blood-volume may elicit a 65 per cent. reduction in the normal flow of blood. On reinjection of an equal amount of gum-saline solution the volume-flow may return to normal. The nutrient-flow (volume-flow × concentration of nutrients in the blood) necessarily increases.

Assuming that the function of a tissue is dependent on the nutrient-flow—hemorrhage and subsequent injection should affect the activity of the gland. Direct experiments show that a continuous secretion of saliva elicited by the intravenous injection of pilocarpin is diminished by hemorrhage and increased by subsequent injection of gum-saline solution.[2]

Observations led me to believe that the conditions in the submaxillary gland hold for the body as a whole and explain the general beneficial effects of injection of inert solution. Nevertheless, experiments were extended to other tissues as well and the same results were obtained.

In muscle, which comprises the bulk of the mammalian organism, hemorrhage and injection elicit like changes in volume-flow of blood. Similarly, the ability of the muscle to respond to repeated stimulation is diminished by hemorrhage and improved by subsequent injection of gum-saline solution.

The basal metabolism of the organism as a whole is likewise affected by hemorrhage and injection. Hemorrhage diminishes and subsequent injection of inert solution increases basal metabolism.

[1] From the Department of Physiology, University of Michigan, Ann Arbor, Michigan.

[2] Though on the whole during acute experiments gum-saline solution appears to improve the general nutrition and function of various tissues, the greatest care should be exercised in the use of this blood substitute in man. Extremely toxic effects with a large drop in blood pressure were not uncommon, even though a high grade of gum acacia and methods of purification were employed.

And, finally, hemorrhage and injection modify pulmonary ventilation—hemorrhage increasing and subsequent injection of gum-saline solution diminishing respiration. In certain instances, when the volume-flow is suddenly accelerated after hemorrhage by a rapid injection of gum-saline solution, respiration may stop for a minute or more. The initial effects are prompt and are produced by an acceleration of unchanged blood through the respiratory center.

The findings above establish a close relationship between tissue function and volume-flow of blood. It seems not improbable that the main effects of hemorrhage and injection are primarily due to changes in the transport of the respiratory gases, oxygen and carbon dioxide. And, if these conclusions regarding the effects of hemorrhage and injection on the gaseous metabolism of the submaxillary gland, striated muscle and the body as a whole are correct, I am inclined to carry them over to the respiratory center as well.

Assuming that hemorrhage leads to an impaired transport of carbon dioxide from the tissues it must also lead to an increased acidity of the tissues. There appears to be no reason for making an exception of the respiratory center. If injection improves the flow of carbon dioxide carriers and the transport of acid from the tissues, it should turn the respiratory center more alkaline in the same way that it turns other tissues more alkaline. I can see no cause for denying the respiratory center the right to live and to metabolize in conformance with the general laws of metabolism. It performs a continuous and most important function and presumably at the expenditure of considerable energy. I, therefore, prefer to look upon the respiratory center as an animate mechanism, having a definite energy exchange of its own, rather than as an inanimate object, operating on the principles of a motor. But admitting that the center possesses a metabolism of its own we must be prepared to accept the consequences. These, perhaps, are summarized in a theory of respiratory control which I have proposed. The theory in brief is this:

The respiratory center possesses an acid metabolism of its own.

The rate of formation of acid in the center and the rate of transport of acid from the center determine the acidity of the center.

The activity of the respiratory center is primarily regulated by the free hydrogen ions which are formed and accumulated within the center itself, as opposed to stimulation by the hydrogen ions brought to the center by the blood.

If living tissues form carbon dioxide in their metabolic processes it must necessarily follow that carbon dioxide flows from the tissues to the blood. This must hold for the respiratory center as well as for any other tissue. Only under special conditions, when the carbon dioxide tension of the arterial blood is increased above that in the respiratory center, can the flow be in the opposite direction. But the carbon dioxide tension of the blood, in so far as it determines the rate of diffusion of carbon dioxide from the center, regulates respiration.

My theory of respiratory control may now be elucidated by a further analysis of the prevailing theories. The theory of the specific stimulating effect of carbon dioxide has gained a number of adherents who have found that the stimulating action of carbon dioxide bears no relation to the hydrogen ion concentration of the arterial blood. For example, the administration of equal amounts of carbon dioxide before and after the administration of sodium bicarbonate elicits equal stimulation, though in the second instance the arterial blood is distinctly more alkaline than in the first. The action of carbon dioxide must, therefore, be specific.

If this be correct it is obvious that the theory of acid control is seriously weakened. But the fact that hyperpnoea is frequently associated with a very low carbon dioxide tension of the arterial blood throws considerable doubt on the importance of carbon dioxide as a specific stimulant.

Several important considerations have been overlooked. The hydrogen ion concentration of a buffer mixture is a function of the relative amounts of acid and base. For example, carbonic acid and sodium bicarbonate of the blood occur in the ratio of 1 to 20 with a pH of approximately 7.35. On the other hand, the acid effect of the blood on the interior of the living cell bears no relation to the acidity of the blood, but rather to the relative rates of penetration of the acid and base. An alkaline solution may exert an acid effect and an acid solution may exert an alkaline effect. Likewise, two solutions of equal acidity may exert different acid effects. Let us take two carbonate buffer mixtures in which carbonic acid and sodium bicarbonate occur in the amounts of 1 to 20 and 3 to 60. They have approximately the same hydrogen ion concentration, yet the second exerts a decidedly more acid effect than the first, due, as Jacobs suggested, to the greater penetration of carbonic acid.

The simplest demonstration of the acid effects of these solutions is to add phenol red and stratify. If they are brought to exactly the same hydrogen ion concentration, phenol red imparts the same color to both. But instantly following stratification there is a display of colors at the interface, indicating that the 1 to 20 solution is turning more acid and the 3 to 60 more alkaline. The effect is due to the relative

rates of migration of carbonic acid and sodium bicarbonate. Assuming that the 1 to 20 solution represents the respiratory center, and the 3 to 60 solution the arterial blood, it is evident that the acidity of the arterial blood is an unreliable index of the acidity of the respiratory center.

Take, for example, the effects of the administration of carbon dioxide and sodium bicarbonate. Carbon dioxide increases the hydrogen ion concentration of the blood, and sodium bicarbonate decreases it. Carbon dioxide invariably increases respiration, whereas sodium bicarbonate may have no effect whatever. The explanation of these dissimilar effects is demonstrated by a special method of recording the hydrogen ion concentration of the blood.

As the present methods for determining the hydrogen ion concentration of the blood are exceedingly unsatisfactory in giving a continuous picture of acid-base disturbances and are very slow in yielding data, I have felt the advantage of developing a continuous method of recording the hydrogen ion concentration of the arterial and venous blood. By means of a potentiometer, a specially devised electrode vessel, and manganese dioxide electrode placed directly in the blood stream, the hydrogen ion concentration is electrometrically recorded (Gesell and Hertzman).

With this method we compared the magnitude of change in acidity of the arterial and venous blood on the administration of carbon dioxide and found that the arterial blood turned considerably more acid than the venous bloods. Apparently the tissues absorbed carbon dioxide and acted as a buffer to the blood. If true, the acidity of the respiratory center must have been increased—accounting for the increased pulmonary ventilation. On the other hand, if we compare the magnitude of change in the hydrogen ion concentration of arterial and venous blood on the administration of sodium bicarbonate—we find the change virtually equal in both, indicating that sodium bicarbonate leaves the blood stream very slowly. If this be true, the injection of sodium bicarbonate has had little effect upon the alkalinity of the respiratory center, which, in turn, accounts for the lack of depression of respiration.

It seems difficult to align much evidence supporting the prevailing theory of regulation of respiration by the arterial hydrogen ion concentration. Perhaps the outstanding evidence is the remarkable constancy of the alveolar carbon dioxide tension and the arterial hydrogen ion concentration during rest, and the augmentation of respiration on the administration of carbon dioxide. But there are so many exceptions to the parallelism between pulmonary ventilation and acidity of the arterial blood that these observations lose their significance. Every form of anoxemia, hemorrhage, uncompensated heart lesion, anemia, etc., accompanied by hyperpnoea, may be associated with increased alkalinity of the arterial blood.

The continuous method of recording changes in the hydrogen ion concentration repeatedly reveals this lack of parallelism between arterial C_H and pulmonary ventilation. On changing from the administration of room air to nitrogen, respiration increases and the arterial blood turns alkaline. And changing back to room air the arterial blood turns acid, and respiration momentarily stops to continue again but at a diminished rate. Repeating the same experiment using pure oxygen in place of room air the results are even more striking. On the final administration of oxygen the increased acidity of the arterial blood is decidedly sharper and of greater magnitude, and correspondingly respiration is more suddenly stopped and apnoea more prolonged.

Hemorrhage offers another good example of the lack of parallelism between pulmonary ventilation and arterial C_H. It evokes increased pulmonary ventilation and is followed by decreased ventilation on reinjection. The increased ventilation is associated with increased alkalinity and the decreased ventilation with decreased alkalinity of the arterial blood. On the other hand, a comparison of the acidity of the venous blood and pulmonary ventilation shows a direct relationship. During hemorrhage the venous blood turns acid and ventilation increases. During injection the venous blood turns alkaline and respiration decreases. This correspondence undoubtedly shows the importance of volume-flow of blood. Though the arterial blood is considerably more alkaline than normal due to its greater ventilation in the lungs, yet when it passes through the tissues it becomes considerably more acid than normal. Hemorrhage undoubtedly increases the acidity of the tissues, indicating the possibility of acid stimulation of the respiratory center.

Further exceptions to lack of correspondence between arterial C_H and respiration are to be found in the experiments on mechanical asphyxia. Following artificial administration of room air the arterial hydrogen ion concentration increases very gradually during mechanical asphyxia, and hyperpnoea occurs with a relatively low arterial C_H. But in mechanical asphyxia following the administration of pure oxygen the hydrogen ion concentration increases to a considerably higher level before the faintest respirations are visible.

However, the theory of the regulative action of the arterial C_H is most generally accepted in the reviews which have recently appeared. As an example

we may cite from the report of the British Hemoglobin Committee:

> A change in hydrogen ion concentration may be the primary cause of the alteration of the activity of the respiratory center. Under other circumstances the primary factor may be either shortage of oxygen or rise of temperature: both these conditions cause increased breathing and therefore will themselves tend to cause alkalemia. Here the change in the reaction of the blood is a secondary factor, but directly it is established its influence will obviously have seriously to be taken into account. The sensitiveness of the respiratory center to changes in hydrogen ion concentration is so great that an apparently trifling alteration of hydrogen ion concentration in the blood may result in great changes in breathing, and as the present methods of direct determination of the hydrogen ion concentration are often of insufficient delicacy to give us the accuracy of measurement that we require we are frequently forced to infer these changes by indirect methods involving measurements of the concentration of CO_2 in the alveolar air, of free and combined CO_2 in the arterial blood, and of the relative excretion of acids and bases in the urine.

And, to quote again in connection with increased respiration in diabetic coma:

> However, it should be pointed out that even if no measurable increase of hydrogen ion concentration is found in diabetic coma, it is possible that the change may be so slight as not to be capable of measurements by the relatively coarse methods at our disposal and it may yet be sufficient to produce the characteristic respiration of diabetic coma.

I am inclined to believe that the evidence for direct regulative control by the arterial hydrogen ion concentration is lacking. The blood is too far removed from the tissues to exert that control. What then is the controlling mechanism? Oxygen undoubtedly plays an important rôle, but the exact mechanism is still debatable. Many observers suggest that lack of oxygen in the arterial blood has a specific stimulating effect on the respiratory center, independent of accompanying changes in acidity. Opposed to this view I have proposed a mechanism by which the supply of oxygen determines tissue acidity including the respiratory center.

Lack of oxygen means diminished oxidation and an accumulation of anaerobic metabolites. In isolated muscle, at least, lactic acid, which is a product of anaerobic metabolism, accumulates in greater amounts; and carbon dioxide, a product of aerobic metabolism, is formed in lesser amounts. The increase in lactic acid being proportionately greater than the decrease in carbonic acid, the rate of total acid production is necessarily greater during anoxemia than under more normal conditions. We have attempted to check these observations on the living animal. Although the complexity of the experiment offers considerable difficulties, the results on the whole indicate increased acid production during anoxemia.

Is the acid metabolism of the respiratory center similar to that of muscle? Dr. McGinty and I have attempted to answer this question. With a single stroke of a guillotine the normal unanesthetized dog was decapitated and the head divided into left and right halves. One half of the brain was instantly frozen in liquid air, and the other half chilled at later intervals varying in different experiments. Analyses of the two halves for lactic acid give both the normal lactic acid content and the rate of formation during lack of oxygen. Assuming the metabolic rate of the brain to be equal to that of the body as a whole, the analyses indicate that the acid production during lack of oxygen is sixteen times as rapid as during normal oxygen supply.

Accepting this assumption and the view that the hydrogen ion is a regulative factor controlling respiration, the probability of acid stimulation during anoxemia even in the presence of alkaline arterial blood must be seriously considered. But even granting a somewhat slower formation of acid during anoxemia the argument still holds. I refer to the disturbance of the coordination of the dual function of hemoglobin, another potent mechanism working towards increased acidity of the tissues. By virtue of the fact that oxidation of hemoglobin increases its acidity and reduction reverses this effect, the transport of oxygen and of carbon dioxide are closely interdependent. The reduction of oxyhemoglobin liberates a base which combines with the carbon dioxide and the HCO_3' ions coming from the tissues, a device maintaining a free diffusion of carbon dioxide and HCO_3' from the tissues to the blood. And, in turn, when the venous blood reaches the lungs oxidation of the hemoglobin increases its acidity and expels carbon dioxide into the alveolar air.

In anoxemia, whatever the type, less oxyhemoglobin is reduced as the blood flows through the tissues, but the production of acids continues. The coordination of the dual function of hemoglobin is broken and the mechanism for the transport of acid is markedly disturbed.

Though an acid mechanism for the respiration seems highly probable it hardly warrants the exclusion of a specific stimulating effect of lack of oxygen. Yet the fact that hyperpnoea from excess of oxygen as well as from lack of oxygen can be explained on the acid basis is rather significant. It is not at all unlikely that the hyperpnoea associated with oxygen

poisoning is a result of a disturbance in the dual function of hemoglobin. Under natural conditions the tissues receive their full supply of oxygen by the reduction of oxyhemoglobin, for the plasma holds very little oxygen in solution. But with excessive oxygen pressure the plasma holds enough oxygen in solution to provide the full quota. As a result —oxyhemoglobin is not reduced, no base is provided to carry the acid from the tissues which necessarily must turn more acid.

My theory of respiratory control may now be summarized.

Changes in the hydrogen ion concentration of the respiratory center rather than of the blood constitute the prime factor in respiratory control.

Since the supply of oxygen determines the absolute and relative amounts of lactic acid and carbon dioxide formed in living tissues, and since it controls the efficiency of transport and elimination of acid, it constitutes the normal and indirect regulator of pulmonary ventilation.

The effects of lactic and carbonic acid are additive. They are exerted indirectly by way of the blood from the tissues, and more directly through their formation in the respiratory center itself.

Diminished oxidation in the respiratory center leads to an accumulation there of the relatively poorly diffusible lactic acid in a relatively poorly buffered cytoplasm and lymph, no longer fully protected by the potential alkalinity of the blood, the dual function being disturbed by the diminution in the reduction of hemoglobin and the liberation of alkali as it passes through the center.

By virtue of its own metabolism and its extreme sensitivity to minute changes in its own hydrogen ion concentration the respiratory center is sensitive to minute changes in its own oxidations, and, therefore, to changes in the tension of oxygen in the arterial blood.

The capacity of the center to respond to changes in the arterial carbon dioxide tension consequent on fluctuations in the general metabolism, however, must also be a factor.[3]

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SCIENTIFIC EVENTS

THE TOTAL ECLIPSE OF THE SUN OF JANUARY 14

THE January issue of *Popular Astronomy* gives an account of the various expeditions which have gone to Sumatra to observe the total eclipse of the sun of January 14. This eclipse promises to be well observed, although the path of totality lies across a part of the globe where there are no established observatories. The eclipse will begin at sunrise in East Africa and the moon's shadow will pass across the Indian Ocean, passing over a small island, Seychelles, about 700 miles east of the African coast, thence across the islands of Sumatra, Borneo and Mindanao, the southernmost one of the Philippine group, the eclipse ending at sunset in the Pacific Ocean.

Most of the observing stations will be grouped on the Island of Sumatra, where the observing conditions appear to be the most favorable, the duration of totality being upwards of three minutes. Unfortunately the maximum duration of 4 minutes 11 seconds occurs in mid-ocean. There will be three expeditions from the United States and one each from England, Australia, Germany, Holland, Italy and Java.

The American parties are: The U. S. Naval Observatory party, in charge of Captain F. B. Littell, including Professors George H. Peters and George M. Raynsford, astronomers in the Naval Observatory, and Dr. John A. Anderson, of the Mount Wilson Observatory. Their observing station will probably be at Tebing Tingge, Sumatra. The Sproul Observatory party, consisting of Director and Mrs. John A. Miller; Dr. Heber D. Curtis, director of the Allegheny Observatory, with Mrs. Curtis and Baldwin Curtis; Ross W. Marriott and Dean B. McLaughlin, of the Sproul Observatory; Adrian Rubel and Wilson M. Powell, seniors at Harvard, and Lamont Dominick, of New York. Their observing station will probably be at Benkoelen, on the west coast of Sumatra. The Harvard party, consisting of Dr. H. T. Stetson, director of the Harvard Astronomical Laboratory; Dr. W. W. Coblentz, physicist of the U. S. Bureau of Standards; Mr. Weld Arnold and Mr. W. A. Spurr, Harvard students. Their station will be at or near Benkoelen.

Dr. Horn d'Arturo, with an Italian expedition, will be stationed in Somaliland, near the east coast of Africa.

The English expedition sent to Sumatra by the "Joint Permanent Committee" will probably be at Benkoelen, a former British naval station. The party consists of Messrs. G. E. Barton, C. R. Davidson, F. J. M. Stratton, F. W. Aston and Colonel J. Whaley Cohen.

The Australian party under Mr. Z. Merfield, of the Melbourne Observatory, will probably be stationed at Benkoelen.

Professor Voûte from Lembang in Java will be near Palembang, north of the mountainous ridge that forms the backbone of Sumatra.

An expedition from the Royal Academy of Science of the Netherlands plans to occupy a station at Ta-

[3] Postgraduate lecture delivered before the Associated Anesthetists of U. S. and Canada, Atlantic City, May 26, 1925. (For references to original articles consult Gesell, *Physiological Review*, 1925, V, p. 551.)