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PHYSIOLOGICAL REGULATION OF THE ACID-BASE BALANCE OF THE BLOOD AND SOME RELATED FUNCTIONS

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Development of knowledge of the blood as a chemical system has of late been rapid and successful. So much so in fact that there seems real danger that the approximately complete solution of one-half of a great problem may be mistaken for a solution of the whole problem: the problem of the regulation of the blood. It is probable that some investigators on this topic (1), (2), (3) do not forget this limitation; but it is quite certain that others do in effect forget that the blood is a physiological fluid regulated by a living organism, and not merely a physicochemical system.

It is true that any one sample of blood, and the gases with which it is equilibrated, consitute a physicochemical system. A large number of its factors, such as chloride, alkali, CO_2, oxygen pressure, etc., are expressible in such dependence upon each other that the alteration of one, such as the oxygen pressure, shifts all of the others. In fact, once a system of this sort is postulated, such interdependence is virtually self-evident. The recent working out of its details affords a satisfactory approach to complete solution of the purely chemical aspects of the problem. All of the alterations of such a system are reversible under the influence merely of the conditions occurring in alternation as the blood passes through the lungs and tissues, and loses or gains oxygen and CO_2 respectively (4).

But not all blood is the same. For instance, the number of corpuscles and amount of hemoglobin is 25 or even 50 per cent greater in one blood than another, or even in a single person at one time (during life in the mountains) as compared with another time. At the same CO_2 and oxygen pressure the other properties would not be the same in these various bloods, but widely different. The diagrams of these

bloods cannot be superimposed. Yet all of these bloods are, properly speaking, normal, or at least necessary, for the individuals in whose vessels they flow. Even a nephritic with so-called "uncompensated acidosis" would probably be very much upset if his blood were suddenly made "normal" for a well person. The attempt to raise a low blood alkali by merely injecting sodium bicarbonate has often proved injurious.

PHYSIOLOGICAL REGULATION. Such facts as these would seem to force recognition of a physiological regulation, a more fundamental mechanism, a superintending nature or physis,[1] determining the particular physicochemical system or interior condition of which the blood should consist at the time. It is this capacity which compensates the exterior conditions, often against the direction in which the latter tend to drive the system. It is not "vitalistic," but merely a frank recognition of fact, to say that the physis, or nature of a living thing, is as much an ultimate reality, as useful and as necessary to physiology, as the properties of the chromosome are for genetics, or those of the atom for chemistry, or of the electron for physics. Doubtless each of these ultimates will be analyzed further mechanistically some day, but each is meanwhile simply assumed in its particular science. Most investigators of the acid-base balance of the blood do not, however, see regulation thus physiologically, but merely chemically. They seem to regard the body as if it were a sort of beaker, or other vessel, containing a standard blood that may be thrown out of normality by the addition of an excess of some constituent. Thus a recent reviewer (5) says in an excellent presentation of this conception: "Only one condition can be considered as normal, that in which both blood bicarbonate and pH are within normal limits."

This conception is erroneous. On the day that these words are written a party of Englishmen is engaged in an attempt to ascend Mount Everest (6). Within a month or two they have ascended from sea level to camps at 17,000 to 23,000 feet. With them are many Tibetan porters, and in neighboring monasteries are monks who were born and who spend their entire lives above 15,000 feet. The blood of all these men contains now only about two-thirds the amount of sodium bicarbonate assumed as normal in the above quotation. In the case of those at the greatest altitude it is only about half the amount

[1] The word physiology is a compound of the Greek words physis and logos. Physis expresses the capacity of the living body to cure itself, that is, to recover equilibrium, often at a new level, which an ordinary machine is rarely able to do.

at sea level. But these men are healthy and normal in any proper sense of the word. Yet if their blood were to be suddenly brought to a sea level content of bicarbonate, they would all be extremely ill. If these Englishmen when they were at sea level two months ago, and in adjustment to a normal barometer, had suddenly been elevated to the high camp on the north col of Mount Everest, they would probably have died within an hour or two. Cases are on record in which balloonists thus suddenly elevated have in fact died (7). But the men on the slopes of Mount Everest are now quite well.

RELATION OF OXYGEN TO BLOOD ALKALI. It will probably contribute to a readier understanding of the facts and physiological relations to be discussed in this paper, if the main point is stated concisely at the outset. It has not become as yet a part of the common working ideas of physiology and biochemistry, but it should. The physiological relations defined by it are not reducible as yet to processes of present day chemistry. But the evidence for the existence of these relations is decisive. The point is this: *The amount of alkali in use in the blood of a healthy individual is fundamentally regulated and determined by the pressure of oxygen in his lungs at the altitude at which he lives. In other words, the type of blood that he has in his vessels at any one time is a function of the mean barometer at the place where he is then living.* Any change in altitude of residence involves a change of oxygen pressure, either up or down. The pressure at the new home induces a slow readjustment of the blood, requiring days or weeks to become complete. This readjustment consists in establishing a new normal amount of blood alkali. We must cease thinking of altitude as abnormal. Denver, a mile above sea level, is just as normal a residence as New York. So also Tibet and Peru, two or three times as high, are normal for their people, or for you, my reader, after a residence of a month or two. A blood alkali of 40, or even 35, is just as normal for a mountain dweller as 50 or 60 is for a sailor; or as 65 or 70 would be if a man lived for a month continuously in a caisson where the air is compressed.

This relation of oxygen to blood alkali is equally important for pathological physiology. It is the key to some of the disturbances of equilibrium (especially in respect to pH) in cardiac and in renal disease. The air-hungry cardiac patient is short of oxygen and suffers virtually from mountain sickness. His blood is rich in corpuscles like a mountaineer. But in other respects his physical defect prevents his attaining complete equilibrium. He strives to compensate, but falls more or less short. On the other hand the nephritic at sea level is under a

barometric pressure which is abnormally high for his blood alkali. The oxygen pressure in his lungs is as great as in his healthy neighbor, whose blood alkali is of normal amount. It will be shown later in this review that this relatively excessive pressure of oxygen is probably the immediate cause of the low pH in his blood. In the cardio-nephritic patient one condition or the other may predominate, or they may alternate, or mingle, not allowing acclimatization, but only partial compensation.

For the healthy man the fundamental regulation in the whole field of the hemato-respiratory functions is the oxygen pressure and supply to which he has become adjusted. The cardiac, nephritic, or diabetic patient strives to adjust, but at the same time is forced out of adjustment. The processes involved are still obscure. All that current knowledge of this matter allows, is the statement of physiological relations. They are important and extensive in their facts, but like most biological and medical phenomena they are not reducible as yet to chemical fundamentals. To pretend that we have the essential point to explain a physiological condition, when we really do not understand it at all, is the surest way of prolonging our lack of understanding. We deceive ourselves when we pretend otherwise.

ERRONEOUS CONCEPTION OF ACIDOSIS. To be more specific: It is time for us to throw off an error of thirty years' standing in regard to "acidosis." Whatever this condition is, it certainly is not merely acid poisoning. A decrease of blood alkali is probably in most cases merely incidental to something more fundamental. An excess of acid is probably not even an essential, or much less a fundamental feature of it, but merely a secondary and not invariable result. In particular "uncompensated acidosis," low pH with low alkali, so far from being uncompensated in a physiological sense, is in fact probably the body's method of seeking compensation.

This amounts to saying that the pH of the blood is not an absolute constant—the body knows none such. Like body temperature, the pH of the blood has only an approximate normal. It is considerably altered from this normal under conditions of strain, such as muscular exercise and fever; and these alterations are probably advantageous.[2] We do not regard 98.6°F., or 37.5°C., as so fixed a constant that anti-

[2] The blood is far more effectively buffered against high pH (alkalosis) than it is against low pH. This is demonstrated by the forms of all the possible CO_2 dissociation curves (see figure). The physiological effects of high pH are also far more severe than those of low pH.

pyretics and ice baths are the simple, universal, and all-sufficient recourse for any and all fever. So it is in regard to the pH of the body fluids. This so-called constant is only one more of the factors which the living system balances against others to maintain the continuity of life and to approximate as nearly as possible to health. Physiological equilibrium and the chemical conception of equilibrium are two quite different things. The one invokes energy to maintain itself, or if disturbed to recover; it makes an effort. The other in seeking balance only goes down hill dynamically. All of this should have been obvious from the beginning. Enthusiasm over the chemical relation which pH expresses has led us to forget the teachings of Claude Bernard (8) and of Haldane (9), the true creed of physiology. Physiological regulation of physiological equilibrium is the essential condition distinguishing a living from a dead system.

Errors such as this arise from the unduly great importance which a new technical conception always assumes in our minds in comparison to the vast amount of things concerning which we are still ignorant. Most reasoning in physiology, perhaps in all science, appears to be by the process which Spinoza (10) termed "Reductio ad ignorantiam." Thus we know that pH expresses the balance of acids and bases in a fluid, and we know that pH is decreased in clinical acidosis. Therefore if decreased pH is not the cause and essence of acidosis, what is? And neither the inquirer, nor the questioned, can answer, our ignorance of any alternative answers for us conventionally. And yet, as in all such questions, the universe undoubtedly holds an indefinite number of other possibilities to us as yet unknown.

ACCLIMATIZATION. To return to our topic. The experience of the Mount Everest expedition indicates that a healthy man may acclimatize quite well to 23,000 feet, barometer 325 mm. There is evidence from other sources (11) to certify that a man when fully acclimatized to any altitude whatever has nearly the same plasma pH. But at different altitudes he has not the same amount of CO_2 either in his lungs or blood. It was first shown by Fitzgerald (12), with Haldane, that the alveolar CO_2 varies with altitude in the same direction as the alveolar pressure of oxygen, or nearly with the barometer. Later I pointed out (13) from data of the Pike's Peak expedition (14) that, when the same men were tested in virtually complete adjustment to altitudes from sea level to 14,000 feet, there was a very close proportionality between the oxygen and CO_2 pressures in the lungs. From these facts it follows that the blood alkali in these men varied always very nearly in proportion to the oxygen pressure. If this were not the case the pH would have had widely varying values in acclimatization to various altitudes.

It is safe to infer that it was nearly constant in the members of the Pike's Peak expedition, at Oxford and New Haven, at Colorado Springs, and after five weeks on the Peak. Thus whenever the residence is shifted up or down, the blood alkali goes slowly down or up, to a new value in a new equilibrium. This new equilibrium is then maintained as was the old, by the regulation of respiration.

HEMATO-RESPIRATORY EQUILIBRIUM. It is essential to keep clearly in mind the constituents of this physiological equilibrium. It includes a chemical equilibrium, but is much more than that. The chemical part (15) has been described so often, and is so well understood now, that it need be only briefly referred to here. But the equally important physiological part is generally misunderstood or ignored.

Chemically, it is the proportion of carbonic acid (H_2CO_3) to sodium bicarbonate, which determines the pH. If the proportion is H_2CO_3:$NaHCO_3$::1:20, or 2:40, or 3:60, or 4:80, the pH is the same. The pH is 7.3, in all these cases. This range from 20 to 80 of blood alkali is greater than actually occurs between an altitude of 23,000 feet and one as far below sea level as the valley of the Dead Sea.

Physically, the carbonic acid of the blood in this relation is determined by Henry's law. The amount of this acid in solution varies in direct proportion to the partial pressure of the gaseous CO_2 in the air of the lungs. A pressure of 20 mm. CO_2 corresponds to 1.5 volumes per cent of dissolved carbonic acid in the blood; 40 mm. pressure causes the solution of 3 volumes per cent; and 60 mm. is in equilibrium with 4.5 of dissolved acid. So in the ratio H_2CO_3:$NaHCO_3$, we could substitute the values for CO_2 pressure (multiplied by a constant) instead of the dissolved carbonic acid, H_2CO_3. This much is well understood. But the next point, at which physiological regulation enters, is equally important and equally quantitative. The relation in this case is an inverse proportion.

Physiologically, it is the volume of air breathed which represents and determines the alveolar CO_2 pressure and the carbonic acid of the blood. It is the breathing that is regulated vitally, and thus regulates the two physical and chemical quantities. The volume of the lung ventilation is the reciprocal of the concentration of CO_2 in the lung air. In principle it is simply a dilution to a greater or less extent. Thus 0.1 liter of CO_2, if diluted in 1.0 liter of air, is 10 per cent; in 2 liters of air, it is 5 per cent; and in 4 liters, 2.5 per cent. The more the ventilation, a, the lower the percentage and partial pressure, b. Thus $a = \frac{1}{b}$.

PULMONARY VENTILATION AND BLOOD ALKALI. How much air does a man breathe? If his body produces the same mass of CO_2 in its metabolism at sea level and on Pike's Peak, or the same mass of CO_2 when healthy and when nephritic, what are the relative volumes of pulmonary ventilation? A healthy man ventilates his lungs at sea level with eighteen units of air for each unit of CO_2 exhaled. This dilution gives a partial pressure of 40 mm. CO_2 in the pulmonary air, a percentage of 5.5 CO_2, and a normal pH. If now the blood alkali is decreased so that his blood contains only $\frac{2}{3}$ the normal amount, he needs only $\frac{2}{3}$ the normal amount of dissolved carbonic acid and $\frac{2}{3}$ the previous alveolar CO_2 pressure to give the normal pH. Accordingly he breathes $\frac{3}{2}$ or 1.5 times as great a volume of air as before, for each unit of CO_2 exhaled. If his blood alkali were for some reason in-

TABLE 1

Showing relations of blood alkali and partial pressures of CO_2 in lung air producing pH 7.3, and the corresponding volumes of breathing

It will be noted that the relation of volume to pressure here is reciprocal, not proportional.

Blood alkali, volumes per cent CO_2	0	7.5	15	30	45	60	75	90
Pressure of CO_2 in lung air, mm...	0	5	10	20	30	40	50	60
Respiration, per cent of resting normal at sea level.....	∞	800	400	200	133	100	80	66
Respiration, liters of air per minute, assuming 6 as normal at sea level.....	∞	48	24	12	8	6	4.8	4

creased 25 per cent above normal, that is to $\frac{5}{4}$ of the normal, the increased amount of dissolved carbonic acid and alveolar CO_2 pressure would be provided by $\frac{4}{5}$, or 80 per cent, of the sea level volume of breathing for each unit of CO_2 exhaled.

From this aspect, the amount of the blood alkali is the factor which controls respiration. In table 1 are shown various amounts of $NaHCO_3$ (expressed in volumes per cent of CO_2). Below each of these figures is given the partial pressure of CO_2 in the air of the lungs, that would maintain the proper amount of carbonic acid (H_2CO_3) in solution to balance the alkali, and give in all cases pH 7.3. In the third line are the relative volumes of ventilation necessary to dilute the CO_2 produced in the body to the concentration shown in the second line. In the fourth line it is assumed, for the sake of illustration, that the individual's

normal breathing at rest at sea level is 6 liters per minute; and to the right and left are shown the volumes corresponding to the figures above them.

But how, it may be asked, is the blood alkali run up or brought down proportionately to the oxygen pressure. In order to understand this, so far as it is understood at all, it will be necessary to give here a somewhat broader statement of the regulation of breathing than merely to say: "Respiration is regulated by CO_2;" or "It is regulated by the pH of the blood;" or "By the blood alkali;" or "By the barometer and oxygen pressure." It is in fact regulated, so far as we can now see, by all of these factors, and doubtless by many more. This is one of the topics on which there has been and still is endless controversy to show that this or that—O_2, CO_2, pH, inherent rhythmicity, and so on—is the fundamental regulator. In the writer's opinion there is no known theory of any great value on this point, because no one has yet attempted to correlate all the data of all the hemato-respiratory functions quantitatively. Merely qualitative conceptions once were useful in this field, but we are beyond that stage now.

REGULATION OF RESPIRATION. Nothing so ambitious as a general theory of respiration will be attempted here; but only a statement of behavior. This behavior, as expressed by the volume of air breathed, is under three controls: 1, The immediate; 2, the intermediate; and 3, the barometric.

1. The first or immediate control of the volume of air breathed each minute is the amount of CO_2, the mass or number of molecules, that metabolism and the degree of muscular activity produce at the time. If twice as much CO_2 is produced during walking as during rest in bed, the volume of air breathed is almost exactly twice as great in the one condition as in the other, as Haldane and Priestley showed (16). This relation in walking and rest holds at sea level, and equally well on Pike's Peak. It maintains a constant alveolar CO_2 at each place.

2. But the alveolar CO_2 is not at all the same for a man at rest at sea level and a month later on Pike's Peak, nor does he breathe the same volume when walking at those places. That relation has been discussed above. We saw there that the relative volumes of air breathed for a given mass of CO_2 exhaled depend upon the blood alkali. If nearly the same pH is to exist in the blood, and if the alkali of the blood on Pike's Peak is only $\frac{4}{5}$ of that at New York, then the breathing must be, and is, $\frac{5}{4}$ or 1.25 times as great at the altitude as at sea level. So it is the blood alkali which serves as the inter-

mediate control of respiration. It sets the degree to which all the CO_2 produced in the body is diluted with air by respiration before it is exhaled from the lungs. Thus for any altitude all these functions and factors are determined by the amount of the blood alkali. It controls the volume of breathing per unit mass CO_2 produced in the body, the alveolar CO_2 pressure, and the free carbonic acid of the blood.

3. The blood alkali in turn is determined in normal persons by the barometer. Thus the oxygen pressure is the fundamental control. But how? What are the processes through which this factor slowly regulates all the others? This problem will be dealt with here from a strictly behavioristic standpoint. It appears to be a relation (of the nature of a normally constant ratio) of the oxygen pressure in the lungs and arterial blood to the blood alkali, or to the concentration of bicarbonate ions [$H\overline{CO_3}$], which determines whether or not physiological equilibrium exists. This relation is disturbed by a change of altitude; for the oxygen pressure is altered. It is also disturbed by the development of heart or kidney disease and by other disorders. In these conditions the blood alkali is the factor that is forced out of adjustment. When the blood alkali is thus lowered it leaves the oxygen pressure relatively too high. It is the direction in which the balance is disturbed that determines whether renewal of equilibrium shall be sought for through a readjustment up or down of all the hemato-respiratory factors.

An unknown factor. I once applied the term "respiratory X" (17) to the unknown factor through which oxygen and alkali act. The value of this factor at any time is the resultant of the antagonistic mass actions of oxygen and alkali. But such a term as "respiratory X" is merely a confession of ignorance. It might be a substance, such as a sulphur-containing body in the blood, or something like it, or the oxidation of sugar in the tissues, or irritation of the vagus endings in the lungs, or certain cells or cell constituents in the respiratory center, its "threshold" (whatever that is materially) or a host of other things. It certainly is not pH nor hemoglobin; but whatever it is, it is as nearly a constant as pH, for at all altitudes the relation between oxygen pressure and blood alkali (or concentration of bicarbonate ions) in the blood of a man acclimatized to that altitude—be it New York or Pike's Peak—is nearly the same. The reason for denying that "respiratory X is merely oxygen want" (18), (19) is that the same pressure of oxygen acts in opposite ways according as the blood alkali is high or low. Respiratory X depresses as well as it stimulates. The oxygen pressure at Colorado Springs, about a mile above sea level, depresses the breathing of a man who has recently lived on Pike's Peak; but it stimulates his breathing if he has just come from sea level; and it neither stimulates nor

depresses his breathing after he has lived at this pressure for a time. In the first case his alkali is low, and his volume of breathing for a time is large. But the oxygen pressure, which is higher than he has been accumstomed to, gradually decreases his volume of breathing and thus increases his alkali until he is acclimatized. In the second case the conditions and processes are exactly the opposite, so his breathing is progressively increased, and this causes a decrease of alkali until acclimatization is complete. It is to be noted particularly in this illustration that the man, whose respiration is here said to be "depressed," actually breathes a larger volume than he in whom this function is here said to be "stimulated."

Regulation of blood alkali by respiration and pH. This ratio of oxygen to alkali appears to be the relation which is primarily upset whenever a change of residence up or down is made. If the oxygen pressure is increased relatively to the alkali, or the latter is decreased relative to the oxygen, the result is a slight depression of the respiratory center and a decrease of pulmonary ventilation relative to the blood alkali. Consequently the alveolar pressure of CO_2 is more than enough to balance the blood alkali. Thus the pH is forced out of its normal value. In the parlance of today an "acidosis" (low pH) is induced, and particularly the state now called "uncompensated acidosis." But this condition tends in a normal organism to call an increased amount of alkali into the blood, to restore a normal pH; thus acclimatization to the lower altitude soon begins to develop. Finally a normal relation is reëstablished between oxygen and alkali, and between the free carbonic acid of the blood and the blood alkali; consequently the pH also again becomes normal, and the volume of pulmonary ventilation then keeps all these factors normal for the altitude.

There is much in this picture to suggest that whenever in disease, whether cardiac, renal, diabetic, or otherwise metabolic, the blood alkali is low in relation to the pressure of oxygen, it is the relatively high pressure of oxygen which causes the slightly depressed respiration, and consequently the abnormally low pH. *Low pH in a fluid buffered like blood can never be due immediately to any other cause than relatively depressed breathing.* A hypopneic pH probably always represents, both in health and in disease, an effort to call more alkali into the blood, just as occurs when a man comes down from a mountain.

An opposite set of processes is called into play when the residence is elevated. The oxygen pressure is then made relatively low as compared to the blood alkali. Accordingly, respiration is augmented so that CO_2 is blown off in slight excess (overbreathing) (20), and the pH is thus made abnormally high. This disturbance of the balance

of carbonic acid and bicarbonate in the blood induces a passage of alkali out of the blood (21), (22). Rapidly at first, then more and more slowly, these readjustments proceed, until acclimatization is attained with physiological equilibrium at the level determined fundamentally by the oxygen pressure.

LAWS OF THE HEMATO-RESPIRATORY FUNCTIONS. The relations above described are of a degree of complexity such that they are scarcely expressible completely and clearly merely in words. They require a more mathematical form of expression. The following restatement of these relations may, therefore, be found useful for intensive consideration.

I. Regulation by the alveolar carbon dioxide. The volume of pulmonary ventilation varies almost exactly in proportion to the carbon dioxide production of the body, and thus holds the pressure of carbon dioxide in the air of the lungs nearly uniform. This is the law of Haldane and Priestley and may be expressed in the roughly mathematical form:

$$\text{Pulmonary ventilation} = CO_2 \text{ produced} \times \left(\frac{100}{\text{alveolar } CO_2 \text{ pressure}} \right) \quad ..(1)$$

In this expression the pulmonary ventilation and carbon dioxide production are the variables and are measured in cubic centimeters or liters per minute, while the alveolar carbon dioxide pressure is measured in per cent of an atmosphere and is a constant for any given amount of blood alkali. The alveolar CO_2 pressure may also be expressed in the denominator in millimeters of mercury, if the mean barometric pressure, minus the pressure of water vapor in the lungs, is substituted for 100 in the numerator.

II. Regulation by blood alkali. Any amount of blood alkali needs a corresponding amount of carbonic acid to balance it so as to give a normal pH. The blood alkali thus determines the alveolar CO_2, and by inverse proportion it thus also adjusts the pulmonary ventilation. It thus sets the dilution ratio, or volume of air breathed, per unit mass carbon dioxide exhaled (as in equation 5). It follows from this that an analysis of the alveolar carbon dioxide pressure and an analysis of the blood alkali afford almost exactly the same information and in only slightly different terms. These relations are demonstrated as follows:

Since from equation (1) above

$$\text{Alveolar } CO_2 \text{ pressure} = \frac{CO_2 \text{ production}}{\text{pulmonary ventilation}} \quad \ldots\ldots\ldots\ldots (2)$$

and since the carbon dioxide dissolved in blood plasma varies with the partial pressure of carbon dioxide in the air of the lungs, that is, by the law of Henry,

$$H_2CO_3 = \text{Alveolar } CO_2 \text{ pressure} \times \text{constant} \quad \ldots\ldots\ldots\ldots (3)$$

and since respiration adjusts the relations of the dissolved to the combined carbon dioxide, so that by the law of L. J. Henderson,

$$\frac{H_2CO_3}{NaHCO_3} = \frac{\text{H-ions}}{\text{a constant}} \text{ and gives a uniform H-ion concentration} \quad \ldots (4)$$

therefore if the right hand term is constant

$$NaHCO_3 = \frac{\text{constant} \times CO_2 \text{ produced}}{\text{pulmonary ventilation}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

III. Equilibrium values of hemato-respiratory factors. The values for the arterial oxygen and CO_2 pressures, and for the amount of blood alkali have very nearly the same proportion to each other at all altitudes, while the volume of breathing per unit mass carbon dioxide produced varies inversely to the other quantities. Thus, if K_1, K_2, K_3, K_4 are constants with the values respectively of 100 mm., 50 volumes per cent, 40 mm. and a dilution factor 18, these being normal sea level values, the law for all oxygen pressures may be formulated thus:

$$\frac{\text{Oxygen pressure in lung air}}{K_1} = \frac{\text{Blood alkali}}{K_2} = \frac{\text{Alveolar } CO_2 \text{ pressure}}{K_3} = \frac{K_4}{\text{Pulmonary ventilation per unit mass } CO_2 \text{ eliminated}} \quad \ldots\ldots\ldots (6)$$

At sea level each member of this equation comes to 1/1; on the shoulder of Mount Everest each would be about 1/2.

IV. The control exerted by oxygen over respiration and thus over pH. Whenever the partial pressure of oxygen in the arterial blood (expressed in millimeters) is above the ratio 100:50, as compared with the alkali (expressed in volumes per cent combined carbon dioxide) respiration is depressed, relatively to the blood alkali, so that the ratio H_2CO_3:$NaHCO_3$, and presumably the H-ion concentration, are raised above normal (low pH). Whenever the oxygen-alkali ratio falls below 100:50, respiration is stimulated, relatively to the blood alkali. Thus the ratio H_2CO_3:$NaHCO_3$, and presumably the H-ion concentration, are decreased (high pH).

V. Regulation of the blood alkali by pH. Whenever a depression of breathing forces and holds the ratio H_2CO_3:$NaHCO_3$ above normal, causing a low pH, an increase of blood alkali tends to occur. Whenever overbreathing holds the ratio below normal, causing a high pH, alkali tends to pass out of the blood. Both processes tend thus to bring the ratio back to normal and to restore a normal pH at a new level of alkali. Thus if the arrow signifies "leads to"

$$(\text{Oxygen: } [\overline{HCO_3}] > 100:50) \longrightarrow \text{Depressed breathing} \longrightarrow \frac{H_2CO_3}{NaHCO_3} \text{ (above normal)} \longrightarrow \text{increase of alkali and thus compensated pH with a higher blood alkali} \ldots\ldots\ldots (7)$$

$$(\text{Oxygen: } [\overline{HCO_3}] < 100:50) \longrightarrow \text{Overbreathing} \longrightarrow \frac{H_2CO_3}{NaHCO_3} \text{ (below normal)} \longrightarrow \text{decrease of alkali and thus compensated pH with a lower blood alkali} \ldots\ldots\ldots (8)$$

This means that the immediate cause of low pH is always a relative depression of breathing, and that the purpose of low pH is to call more alkali into the blood; while the immediate cause of high pH is always overbreathing and its purpose is to drive some of the alkali out of the blood. (For a fuller statement of these relations, see the series of papers on Hemato-Respiratory Functions, by Haggard and Henderson, Journal of Biological Chemistry, Vols. 39–47, 1919–21, and also those on the Respiratory Regulation of the CO_2 Capacity of the Blood, same journal, February, 1918, Vol. 33, p. 333.)

IMMEDIATE CAUSE OF LOW pH. It may be well to explain what this discussion just here is aiming at: It is to show that acidosis, in the sense of low pH, is simply depression of breathing; and that its more fundamental causes lie therefore somewhere in the regulation of respiration. The conception is now prevalent that when the balance of acids and bases in the living body is upset, an excessive production of acids is necessarily involved. It is now generally believed that the clinical condition called "acidosis" is, therefore, essentially the same as that which can be produced by injecting acids. The best experimental parallel is that effected by J. B. S. Haldane (23), who swallowed considerable amounts of ammonium chloride. The ammonia was converted into urea and excreted, while the hydrochloric acid accumulated in the body. Consequently the sodium bicarbonate of the blood was lowered to such an extent that, as J. S. Haldane (24) (his father) recently remarked, "I was almost ashamed to walk with him at a leisurely pace along the streets of Oxford, for he was panting so hard as to attract everyone's attention."

The general conception of poisoning with acid originated long before physical chemistry had reached the point of expressing an acid-base balance by its hydrogen ion concentration (or its clumsy negative logarithm) pH. When it was found that the pH of the blood in clinical acidosis is low, the simple inference (by the reductio ad ignorantiam) was therefore that acid elements predominated in the blood. According to that view, that is virtually all there is to it. This would be the case if the blood were in a beaker, under a bell jar, in a thermostat.

But in the body in addition to structures and arrangements corresponding to the beaker, bell jar and thermostat, there is a regulating device, one of many, the respiratory center. This device normally adjusts the ventilation of the living bell jar, the alveolar air of the lungs, so that the concentration of CO_2 in the air has not a fixed absolute value, but a fixed value relative to the amount of sodium bicarbonate in the blood. The nature of the blood, both in the beaker and in the body, is such that the only free acid that can ever occur is H_2CO_3.

Its amount is directly proportional (by Henry's law) to the concentration of CO_2 in the equilibrating air. Furthermore, the pH is the immediate resultant of only two factors, $NaHCO_3$ and H_2CO_3. If both are normal, pH is normal; if both are twice normal, pH is still normal; if both are half normal, pH is nevertheless normal.

Now suppose a chemist with such a system set up in his laboratory suspected that something had happened by which a little acid had been added, or a little alkali withdrawn from the contents of the beaker. He would determine the amount of $NaHCO_3$, and perhaps find his suspicion confirmed. But he would not expect to find the pH altered. On the contrary he would expect to find the ventilation increased, so that the concentrations of CO_2 in the air and of H_2CO_3 in the blood were lowered in exact proportion to the decrease of alkali.

But suppose that he finds that the pH is in fact lowered. This is usually the case in clinical acidosis. What inference should even the chemist, or certainly a physiologist with regulation as a creed, draw from this alteration of pH? Only one conclusion is possible; namely, that the mechanism regulating the atmosphere in the bell jar has been in some manner depressed. In other words, let the fundamental cause by what it may, the only possible immediate cause of a low pH in the blood in the living body is a relative depression of breathing, with the emphasis on the word relative.

Let us see how much of a relative depression of breathing would have such an effect, and how much of an increase of ventilation would give a normal pH again. This is the more important because the ventilation is in fact continually varying with every bodily movement throughout life. Yet it is often treated, or neglected, by workers in this field, as if the volume of air breathed were almost as rigid a constant as a man's height.

QUANTITATIVE RELATION BETWEEN VOLUME OF BREATHING AND pH. It is quite easy to make this estimate by means of the CO_2 diagram introduced by Haggard and the writer (25), also independently by Straub and Meier (26) in Germany, and slightly modified by Van Slyke (27) (see fig. 1). This diagram evaluates all points in the CO_2 dissociation curve of the blood in three respects: 1, the amount of combined CO_2 and the alkali in use, in other words the $NaHCO_3$; 2, the pressure of CO_2 in millimeters and therefore the amount of carbonic acid, H_2CO_3, in solution; and 3, the relation of carbonic acid to bicarbonate, in other words, the pH. The scales for these quantities

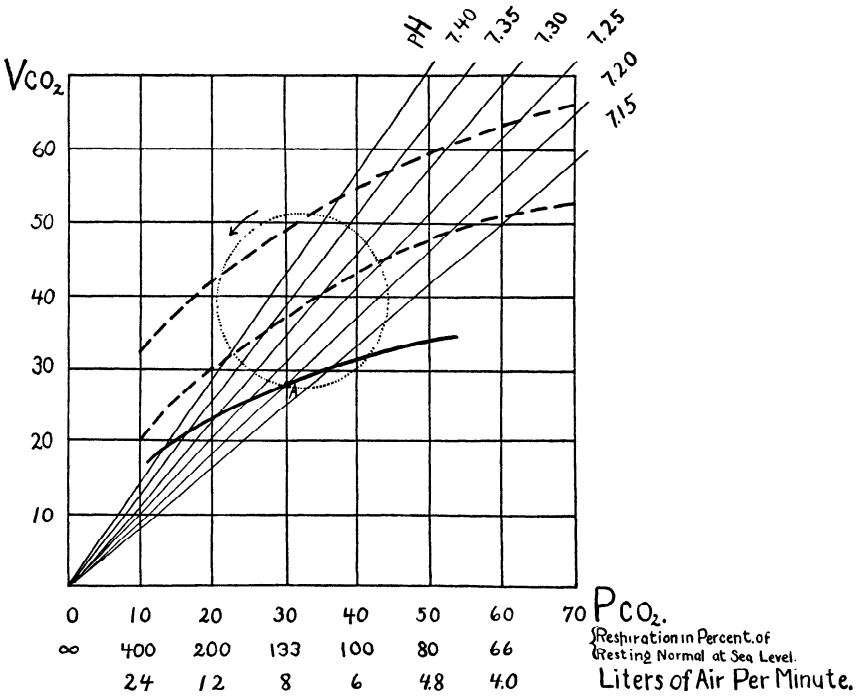

Fig. 1. *The CO_2 diagram.* The point marked *A* indicates the condition of the arterial blood. It lies upon the CO_2 dissociation curve, the solid line, which expresses (by the scale at the left) the alkali available in the blood, its CO_2 combining power, at the time. The point on the curve at which *A* is held is determined by the pressure of CO_2, according to the scale immediately below the abscissa. In the next scale below are given the volumes of breathing, and below that the number of liters of air per minute in the breathing, which would give each particular pressure of CO_2 and would hold the arterial blood, *A*, at corresponding points on the dissociation curve. The oblique lines express the pH for the points at which each intersects the dissociation curve. The broken curves indicate the limits of normal variations in the amount of blood alkali in healthy people at sea level. From this it is seen that the dissociation curve here indicated expresses a low blood alkali, and the *A* point lying on the line of pH 7.2 indicates so-called "uncompensated acidosis." If the volume of breathing were increased from 8 liters up to 12 liters, *A* would lie at the intersection of the dissociation curve and the normal pH line 7.3. The circle indicates the general character of the movement of the *A* point during acclimatization to altitude, and after return to sea level. This movement to the left and down and then to the right and up again is due both to movement of *A* along the CO_2 dissociation curve and to a rise or fall of the curve itself. It expresses the decrease of blood alkali when a man goes up to a greater altitude to live and the increase again when he returns to sea level. The rotation is counterclockwise, indicating that when breathing is stimulated by less oxygen, the *A* point is moved to the left, or alkaline side of normality, and the alkali falls, carrying the *A* point down with it. When, on the contrary, respiration is depressed by a relative excess of oxygen, as in a mountaineer who has come down to sea level or in a nephritic at sea level, the *A* point swings to the right or acid side of normality in the attempt to call an increased amount of alkali into the blood.

are shown by the ordinate, the abscissa and the radiating transverse lines respectively.

Now let us add to this figure two other scales to show the relative volumes of pulmonary ventilation and the amount of respiration involved. The quantities are taken from the table (page 137). Let us call the volume of air breathed 100, when the alveolar CO_2 is 40 mm.; then let us set the figures for the volumes of breathing under all the other alveolar CO_2 pressures. This has been done in the figure here shown. Moreover, assuming the breathing to be 6 liters per minute, when the individual is healthy and at rest at sea level, we can also predict the volumes of air that he would breathe at any and all other pressures of CO_2 in the lung air. These volumes, in liters of air per minute, have been noted below the abscissa of the diagram.

On the CO_2 dissociation curve shown in the diagram the point at which the breathing was holding the arterial blood has been marked *A*. More ventilation would move this point to the left along the CO_2 dissociation curve, and less ventilation would move it to the right. The curve indicates an abnormally low blood alkali, for the similar dotted curves above it are the limits of normal variation at sea level. At a volume of breathing of 7 liters per minute or 36 mm. CO_2 pressure, the CO_2 dissociation curve crosses (approximately) the line of pH 7.15. According to the diagram, 12 liters per minute of breathing would give an alveolar CO_2 pressure of 20 mm., and at this pressure the dissociation curve indicates that the pH of the blood would be 7.32. Actually a nephritic or diabetic with the low alkali here shown usually has a pH distinctly below normal, and his condition is termed "uncompensated acidosis." But be it noted from the diagram: he need only breathe 12 liters of air, instead of the 8 or 10 that he does breathe, to effect full compensation in respect to pH. There is no mechanical difficulty about breathing this volume; anyone who takes a walk breathes as much as that. He could, but does not; and the fact that he does not is the immediate cause of the low pH. Absolutely his breathing is much above normal, it may be 8 or 10 liters instead of 6. But relatively it is nevertheless depressed below the volume (12 liters) that it should have at the existing blood alkali.

May it not be that, his alkali having been lowered in some way, the high relation of oxygen to bicarbonate induces a relative depression of breathing? Inhalation of oxygen has this effect gradually on a normal man. On general physiological principles of regulation is it not probable also that the low pH represents an effort to call more

alkali into the blood? So to speak, he has a Pike's Peak blood alkali and a sea level oxygen pressure. I think that both these questions may be safely answered in the affirmative. The figure shows that any reasonable degree of low blood alkali can easily be compensated by a quite feasible increase of breathing. It shows that the breathing that would give the pH found clinically, and that which would give a normal pH, are not so different in volume as to involve much additional strain on respiration. Extreme conditions which involve a blood alkali below 20 are almost always rapidly fatal, for these require a volume of breathing which it is not possible to maintain indefinitely. But for all ordinary degrees of "acidosis" in the sense of low blood alkali, the immediate, sufficient and sole cause of the low pH is the (relative) depression of the respiratory center and of the volume of breathing.

Some of those who neglect respiration as a factor in this relation are led, quite unconsciously, to state impossibilities, and it is evident that most readers of the biochemical journals now see nothing incongruous in such statements. For instance, we are informed that in ether anesthesia the "excitement hyperpnea" involves a great increase of pulmonary ventilation, while the production of CO_2 may even be lessened by the anesthetic; and yet (they say) there is also a rise of CO_2 tension in the arterial blood, and this rise is a factor, along with a slightly lowered alkali, in causing the hyperpnea. A wonderful trap for the unwary is that negative logarithm of the figure obtained by dividing the blood alkali into the tension of CO_2 and multiplying by a solubility constant and then by another factor (K, supposed—perhaps erroneously—to be constant); all of which is pH. It becomes indeed the classic "pons asinorum" when we substitute for the tension of CO_2 the reciprocal value for the volume of breathing per unit mass CO_2.

But suppose we were told (e.g., by some university official) that simultaneously with a rise of prices of food and clothes, and possibly a slight decrease of professors' salaries, the said professors and their families would be able to live in greater affluence than at present. In this case the reciprocal relation of prices to affluence would not be as difficult to keep in mind as that between pulmonary ventilation and the tension of CO_2. But then we do not forget prices, as we do forget the volume of pulmonary ventilation; nor do we confuse ourselves by using the negative logarithm of the ratio of the goods on the market to the quantity of money in circulation.

In our field it would be better to use the direct figures for H-ion concentration. I would again suggest the form of expression cH7 = 0.5, or cH6 = 0.8 and so on, as a short way of writing $cH = 10^{-7} \times 0.5$, or $cH = 10^{-6} \times 0.8$ etc. This form is as short as that of pH. It means that the actual H-ion concentration, if multiplied by the power of ten indicated at the left of the equal sign, would amount to the fraction of a mol shown by the decimal at the right of the equal sign.

DEFECTS OF PRESENT THEORY. One of the striking defects of the acid poisoning theory is that blood alkali and the H-ion concentration

are not proportional functions. In most biochemical writing they are still treated as if the alkali and pH must always rise and fall together. So in 1919, Haggard and I introduced the CO_2 diagram (see the figure) for the purpose of demonstrating graphically that while blood alkali varies up and down, pH swings round on the arc of a circle. But this demonstration had little effect. The conception that acidosis is simply neutralization of bicarbonate by acid is still strongly held. A closely similar graphic expression is now usually employed as demonstrating the purely chemical basis of acidosis.

Another striking defect of the chemical theory is that in some conditions of clinical acidosis, the only evidence that the blood alkali has been neutralized by acids is that the alkali is low. Consider the nephritic type. The normal kidney has as one of its chief functions the adjustment of the osmotic pressure of the blood. The diseased kidney may not excrete chlorides as efficiently as normally, and attempts to compensate by excreting other substances instead. Some recent developments (28) suggest such a possible explanation of the low blood alkali in nephritis, which is at least as probable as the theory by which the body of the nephritic is supposed to produce an excess of acids. For the acids are undiscoverable, and a decrease of blood alkali in any other way would have the same result: namely, a call for a decrease of carbonic acid and an increase of breathing to bring it about, so as to prevent an extreme disturbance of pH. To a considerable degree the breathing is increased, but not enough to restore an entirely normal pH. The pressure of oxygen is now abnormally high in relation to the alkali, and this relation tends to depress respiration sufficiently to cause a distinctly low pH. The patient, therefore, breathes a larger volume of air than if he had a normal blood alkali, but not a sufficient volume to exactly balance the alkali. As pointed out in a previous section, he is like a man whose blood alkali is that of a great altitude, but who never succeeds in attaining complete acclimatization because the oxygen pressure is that of sea level where he lives.

The present confusion in this field results largely from the use of the word "acidosis" in several different senses: 1, the clinical condition; 2, low pH; 3, low alkali bicarbonates, or low CO_2 capacity, or low "alkaline reserve"; 4, ketosis. The word "acidosis" should be used only in the first of these senses, a symptom complex. The second should be called "hyperhydria" or "relative hypopnea"; for the latter term would indicate the immediate cause of the condition, while the expression "uncompensated acidosis," now generally used, fails to remind us what function it is (namely respiration) that is not compensating. The third is now denominated "hypocapnia" in the current German literature and

should be so called in our journals also. The use of this term should indicate merely that the CO_2 of the blood, that is, the bicarbonate content, is low; but with no implication as to how this condition is caused in the particular case; so that it may not be confused with a simple acapnia from overbreathing. The various senses of "alkalosis," as the term is now used, would then be denominated "hypohydria," for high pH, and "hypercapnia" for high alkali bicarbonates.

The theory of acid poisoning as popularly used rests largely upon the term "alkaline reserve (29)." This expression served at first a very useful purpose in calling attention to an important and measurable property of the blood. But it almost deserves to be classed with "phlogiston" in the extent to which it has misled thought. It is only just to add that Van Slyke, who introduced this term, has done more than anyone else to demonstrate that by far the greater part of the acid neutralizing power of the blood, the true alkaline reserve, is really afforded by the hemoglobin alkali of the corpuscles, and relatively little by the sodium bicarbonate of the plasma.

So long as the expression alkaline reserve is used to denote bicarbonates it must continue to mislead by suggesting that it is the $NaHCO_3$ of the plasma which neutralizes any acid administered by mouth or intravenously or that may be formed by some perversion of metabolism. Araki (30) found many years ago that after asphyxia, especially from carbon monoxide, lactic acid occurs in the blood and urine. It was, of course, wholly in the form of sodium lactate, for the free acid in appreciable quantities can never occur in a system buffered like blood. The Hill-Meyerhof (31) conception of muscular contraction makes lactic acid the essential factor in every bodily movement, and suggests an escape of the excess from the muscles into the blood during intense exertion. This escape has been verified by Barr, Himwich and Green (32). They have shown that the blood alkali is distinctly decreased for some time after strenuous muscular work. It has seemed logical to determine the amount of this decrease in per cent of a mol and the amount of lactate in the same unit, and to compare the figures. When this comparison is made the amount of lactic acid is generally found to be too small to account molecule for molecule for the neutralization of $NaHCO_3$. But suppose the figures exactly balanced, would that show that there is a simple lactic acid acidosis after exercise? Many recent writers with the alkaline reserve in their minds have discussed this and related questions (e.g., ketosis) as if the logical answer were in the affirmative. In fact, however, if lactic acid or any other strong acid is added to blood, most of the alkali which neutralizes it is drawn

from the hemoglobin alkali reserve; and it causes, therefore, only a very slight decrease in the plasma bicarbonates. As Haggard and I pointed out, measurement of the "acid load of the corpuscles" (33) would be a much truer index of the decrease of the real alkaline reserve of the blood than the usual determination of plasma bicarbonates. Bock, Field and Adair (34) have recognized and applied essentially the same idea and find the diminution of bicarbonates is not a valid index of the amount of acid in the blood. Thus even on strictly chemical grounds it is erroneous to conclude that a reduction of 10 or 20 per cent in the blood alkali (combined CO_2) is due to lactic or any other acid, unless many times as much of that acid in neutralized form can be found in the blood and urine as would correspond to the reduction of alkali on a molecule for molecule basis. The same relations and the same reasoning apply also to the decrease of bicarbonates in ketosis.

In all such cases the "reductio ad ignorantiam" lead to the question: If the decrease of blood alkali is not due to neutralization by acid, to what else can it be due? No answer has been forthcoming, so lactic acid acidosis has been considered to be proved. In fact, however, the comparison of the amount of lactate and the amount of decrease of blood alkali (or combined CO_2) is sufficient evidence to prove that whatever the "acidosis" really is, it certainly is not due merely to a flooding of the blood and neutralization of its $NaHCO_3$ by lactic acid. Another possible and more probable direction in which an explanation may be sought will be suggested hereafter.

DEFECTS OF THE CAPNIAL THEORY. The general conception of the regulation of the acid-base equilibrium of the blood which has been set forth in this review may be called the capnial theory (35), in contrast to the acid poisoning theory. The latter will probably be either discarded or greatly modified, and indeed it is constantly being modified in respect, for example, to the real alkaline reserve. But it must be freely admitted that the capnial theory is also still very defective in important particulars, and that some conditions predicted from it have been proved by competent investigators to have quite different values from the predictions. When this theory was formulated, essentially as here stated, some years ago by Haggard and myself (25), we believed that it afforded a nearly complete explanation of all the acid-base adjustments and readjustments in the blood. It appears to accord quite well with the conceptions regarding adjustment to altitude now used by all workers on that problem (11), (12), (14), (20), (24), (36). But we believed also that it explained the disturbance of equilibrium

and the readjustments occurring in anesthesia. From the theory, as expressed in the CO_2 diagram, it appeared to us that during the stage of respiratory excitement the pH and the A point on the dissociation curve should be forced over to the alkaline side. This would drive alkali out of the blood and lower the dissociation curve. During recovery the pH and A point would move to the acid side of normal, because of the depression of breathing, and alkali would thus be called back into the blood. The pH and A point in the CO_2 diagram would thus revolve counterclockwise in a roughly circular path and would control the passage of alkali out of the blood and into it again. In fact, however, several investigators (37) have shown that in anesthesia the pH or A point is continually on the acid side of the normal pH. Evidently the influence of anesthesia in respect to disturbance of pH is exerted, not only through the respiratory center, but also through some influence upon the tissues (probably upon the oxidation processes) causing them to draw alkali out of the blood, or to discharge phosphoric acid into the blood, as Stehle and Bourne (38) find.

This matter might seem to be one of purely theoretical interest. In fact, however, it is of so much practical importance that a large number of lives and several years of progress have been lost because of the difficulties which the current conception of "acidosis" has opposed to an adequate practical trial of therapeutic measures based on the capnial theory and in accord with the experiments on which it in turn is based.

Experimentally, Haggard and I (21) found that inhalation of CO_2 in slightly more than the alveolar concentration was a very effective method of restoring a low blood alkali to normal after anesthesia, or "calling alkali back into the blood," as we expressed it. We tried this procedure at first very cautiously, then more and more confidently on patients after prolonged surgical operations and profound ether anesthesia administered by the drop method (39). The clinical effects of this use of CO_2 inhalation were brilliant, a result confirmed by White (40).

We then tried with success inhalations of CO_2 and oxygen, or even CO_2 in air, for the treatment of carbon monoxide asphyxia. Carbon monoxide asphyxia is par excellence the classic form of "asphyxial acidosis." In it, if in any condition, should be found that "self poisoning by acids from incomplete oxidation in the tissues," which the current theory of acidosis postulates. Nevertheless our experience has demonstrated that in the treatment of carbon monoxide asphyxia, if one had to choose between pure oxygen without CO_2, and CO_2 in air with no

addition of oxygen, the latter treatment would be much the more effective even in overcoming acidosis (41), (42).

With these results established both experimentally, and now on an extensive scale clinically, in respect both to anesthesia and asphyxia, it might be supposed that it would have been easy to bring about the introduction into practical therapy of CO_2 inhalation. But it happened on innumerable occasions throughout many years that, just as success seemed to be at hand, we were stopped because the clinician with whom we were coöperating was informed by some biochemist that: "During and after anesthesia, and particularly in asphyxia, there is a condition of acidosis. The alkaline reserve and pH are subnormal, indicating an excess of acids. Obviously, therefore, to administer CO_2 and thus increase the acidity of the blood still further is unjustified and in fact distinctly and strongly contraindicated." Truly a little knowledge of physical chemistry is a dangerous thing in the interpretation of vital processes.

The use of CO_2 inhalation in connection with anesthesia, especially after ether, has now proved in practice so advantageous that anesthetists are very generally and increasingly using it. Furthermore the inhalation of oxygen plus 5 per cent CO_2 for the treatment of carbon monoxide asphyxia, has come into wide use (42). It has to its credit already the saving of a large number of lives. Of course the oxygen is responsible for much of the benefit of this inhalation and the CO_2 serves as a respiratory stimulant. But experiments on animals show conclusively that among the effects of CO_2 inhalation are restoration of a normal blood alkali, and probably of other interior conditions, even apart from the effects on respiration. Results on patients support this view. A workman is lifted out of a trench in the street or dragged away from a blast furnace; he is wholly comatose from carbon monoxide and scarcely breathing. He is given an inhalation of oxygen and 5 per cent CO_2 for perhaps a quarter of an hour after which he is not only conscious again, but ready to go back to work, feeling well and actively exerting himself. Longer asphyxia involves slower recovery, but the results are equally efficacious. Official reports of such cases, and sometimes of many such cases, come to us nearly every week. They indicate that the inhalation of oxygen and CO_2 does something more than merely to displace carbon monoxide from the blood. In experiments on men gassed up to 30 or 40 per cent saturation in this laboratory, no one who has not received CO_2 has ever felt like going back to work the same day. The early stages of carbon monoxide asphyxia

always involve much overbreathing. We originally thought that the resulting simple acapnia was the direct cause of the lowered blood alkali. It must be admitted now, however, that it is more probable that the withdrawal of blood alkali into the tissues is the result of tissue asphyxia. One result noted here is cerebral edema (43). Another is pulmonary congestion. Both are counteracted by oxygen and CO_2 inhalation. Whatever the explanation may be, the decrease of CO_2 in the body, decrease of both carbonic acid and bicarbonates, appears to be an important element in carbon monoxide asphyxia; and the restoration of this carbon dioxide to the body is an important element in effective therapy both after asphyxia and anesthesia.

SOME IMPORTANT, BUT NEGLECTED PHENOMENA. The problems discussed in this review require for their solution, not only the physical chemistry of the blood, but a much more extensive consideration of respiratory behavior than is usually brought to bear upon them. Many of the respiratory reactions are indeed difficult to explain, or at present even to harmonize with each other. But that does not justify ignoring them. Some of the phenomena, which are especially enigmatic or paradoxical are as follows:

A. If a normal man inhales a few breaths of nearly pure nitrogen a vigorous hyperpnea immediately results. It is a well-established fact that there is an interaction of oxygen and CO_2 upon hemoglobin, by which the removal of oxygen enables the blood to carry CO_2 more easily, that is, at a higher pH. The blood is therefore presumably suddenly rendered very much more alkaline than normal by the nearly complete removal of oxygen. Nevertheless hyperpnea is induced instead of apnea, as might be expected on the analogy of the effects of voluntary forced breathing. Evidently low oxygen does not act on respiration directly through pH.

B. If a normal man breathes air containing even 2 or 3 per cent less oxygen than normal (18 per cent instead of 21), his respiration usually exhibits after a time an increase of the volume of air per unit of CO_2 exhaled. If we compare the pressure of oxygen in the lungs in this condition and the pressure when normal air is breathed, and apply these pressures on the oxyhemoglobin dissociation curve, the difference in the indicated oxygen content of the arterial blood is very slight. It would seem logical, therefore, to infer that the stimulation induced by slight oxygen deficiency is due to decrease in the pressure of this gas dissolved in the blood rather than to a decrease in the amount (in volumes per cent) held by the blood.

C. Contrary to the view just stated, however, if the man is made to breathe air which is normal except for the addition of 0.01 to 0.04 per cent carbon monoxide, so that his blood after a time is 10 or 15 per cent saturated with this gas, the volume of breathing is also distinctly augmented per unit of CO_2 exhaled. In this case, however, the oxygen pressure in his blood is normal, or is even increased above normal by the slight hyperpnea. At the same time the oxygen carrying capacity of the blood is so slightly decreased that it seems impossible that the venous blood from any tissue can actually be depleted of oxygen, and

yet the effect on respiration is essentially the same as that of a slightly decreased pressure (as in *B*).

D. The breathing of low oxygen, or low atmospheric pressure, or carbon monoxide asphyxia do not decrease the amount of oxygen consumed even when the stage of coma is reached. On the contrary the oxygen consumption continues at almost the basic rate, or is even slightly increased by the muscular activity of breathing, until the degree of saturation of the blood is such that the venous blood is entirely depleted of oxygen and death is at hand. The idea that the effects on breathing and on blood alkali induced by the conditions above noted (*B* and *C*) are due to an absolute deficiency of oxygen is, therefore, very improbable (45).

E. When a dog is kept in a chamber containing air to which 0.1 or 0.2 per cent carbon monoxide has been added, it develops the initial symptoms of asphyxia, especially hyperpnea, and becomes groggy. If at that stage it is removed to entirely fresh air it is liable to collapse. City firemen and the men on mine rescue crews are well acquainted with this effect of fresh air on a man who has been working in smoke. Until recently no one had even suggested an explanation of these phenomena. Haldane (44) has now suggested that it is the CO_2 in smoke which keeps the men up, and that it is the lack of CO_2 which is the final element in the collapse in fresh air.

F. When a dog is kept in air to which enough carbon monoxide has been added to produce a very considerable, but not fatal, degree of saturation of its blood, it often happens that the animal collapses; but after a time a considerable degree of recovery may occur. The animal may not only recover consciousness, but may even walk about the gassing chamber in which a short time previously in the same atmosphere it had lain in a state of coma. It is upon such phenomena as these (although not quoting this particular occurrence) that Haldane (24) bases his belief in an active secretion of oxygen by the lungs as a factor in acclimatization to extremely high altitudes and to oxygen deficiency in general. Perhaps the accumulation of CO_2 in the chamber is also a factor.

G. When muscles are worked intensely the effect upon respiration is much greater than the gaseous exchange warrants (as Zuntz (46) showed), and distinct overbreathing may be induced. This phenomenon is most striking at low oxygen pressures or after partial saturation of the blood with carbon monoxide. Men out of training overbreathe much more than do athletes for an equal exertion (47). The shortness of breath of cardiac patients is similar. (Overworked muscles seem to produce respiratory X; but this statement merely denies that the overstimulation of respiration is due to CO_2, or in the main to lactic acid. According to Haldane's view, the overworked muscles produce also the something which causes active secretion of oxygen when the blood from these muscles reaches the lungs. Whether or not the two hypothetical explanations here mentioned are correct, the phenomena are real and require not denial but study and explanation.)

H. When both vagi are divided (in a dog under local but no general anesthesia) it is found that inhalation of CO_2 still produces almost as distinct augmentation of the volume of breathing as was the case prior to the section. In the experience of this laboratory, however, the breathing of air low in oxygen has

little and sometimes no perceptible effect on respiration after vagus section. The same is true of the induction of carbon monoxide asphyxia; although both of these conditions cause hyperpnea in the intact animal. The respiratory rhythm and volume after vagus section may continue almost unaffected up to the point of fatal asphyxia. The blood alkali in these cases usually continues to be normal up to the end (45). This is crucial evidence against the present general conception of the relation of acidosis to oxygen deficiency.

Such phenomena as these require to be considered, explained and harmonized before the behavior of the hemato-respiratory functions in health and disease can be regarded as solved. Such problems certainly are not solved by merely referring them wholesale to disturbance of pH. Nor are they solved by transferring them to the respiratory center itself. (Gesell, this volume.)

OXIDATION OF SUGAR IN THE TISSUES AS A CONTROLLING FACTOR IN THE REGULATION OF BLOOD ALKALI. The deficiencies above shown in both of the theories, in respect to the part played by the tissues in the causation of low blood alkali, indicate that the time is ripe for the formulation of a conception on that point more nearly adjusted to the present state of information. Such a formulation, on the basis of present data, will necessarily leave many of the physiological reactions above mentioned still unexplained; but it will assist in the attainment of new knowledge by serving as a *corpus vile* on which investigators may operate to show wherein and to what extent it is wrong. For this purpose the following propositions may serve: When the blood alkali is decreased in such conditions as diabetic acidosis, or as a result of carbon monoxide asphyxia, or general anesthesia (e.g., with ether) or after vigorous muscular exercise, the chief process involved is the withdrawal of alkali from the blood into the tissues; for the amount of (neutralized) acid found in the blood is usually slight in comparison to the decrease of the alkali of the corpuscles and plasma bicarbonate. The condition chiefly determining the extent of this withdrawal of alkali, or its return to the blood, is the freedom with which sugar is oxidized in the tissues. Among the essential factors are an adequate supply of sugar, an ample supply of oxygen, and sufficient insulin to facilitate the process. Deficiency in any of these factors leads to withdrawal of alkali from the blood into the tissues. In the dynamic equilibrium of this process the mass action of oxygen is balanced against the mass action of bicarbonate ions, and the H-ion concentration is a variable dependent (through respiration) upon the ratio of oxygen to bicarbonate and tending to restore that ratio to normal by the shift of alkali from blood to tissues and vice versa.

The form of buffering occurring in the tissues, for example in muscle,

is not so well understood as that in blood, but it appears to consist largely of proteins serving as weak acids and combined with inorganic alkalies. The condition would thus be analogous to the hemoglobin-alkali which is the chief factor in the buffering of the blood. It would exceed the scope of this review to discuss this topic extensively but some recent investigations which seem to be in accord with the formulation presented in the previous paragraph may be mentioned.

Benedict and Talbot (48) have shown that in children the reserve of sugar is much more rapidly exhausted than in adults; and Talbot, Shaw and Moriarty (49) find that hypoglycemia due to fasting produces a definite acidosis which quickly clears up on administration of even a small amount of sugar. They conclude that clinically when a ketosis is found it must be assumed that there is some interference either with the availability of the sugar or with the ability of the body to oxidize sugar. If the body is able to oxidize sugar, as is the condition in fasting children, then the ketosis must be due either to a sugar deficit or a lowered availability of the sugar deposits of the body. Clinically, the administration of glucose to a child with acidosis is usually all that is necessary to correct the symptoms of this condition if the supply of water also is ample.

The clinical experience and experimental work of Banting and his associates (50) appear to demonstrate that insulin promotes the combustion of glucose. Bock, Field and Adair (34) find that even in diabetic coma the administration of insulin and sugar may be largely effective in overcoming the clinical symptoms and restoring a normal blood alkali. It appears from the observations of John (51) among others that insulin does not act in the blood; presumably its action is in the tissues.

Allen (52) reports observations on puppies closely similar to those above noted in children. Acidosis is induced by sugar depletion and relieved by sugar administration. He shows both by experimental evidence and from clinical facts that low blood alkali is merely a concomitant and not the essential factor in acidosis as a clinical entity; and he urges a broader view than merely that the condition consists in a neutralization of the body's store of alkali by acids.

The work of Shaffer (53) dealing with the ketogenic-antiketogenic balance indicates a line along which much valuable information is accumulating. Allen justly remarks, however, of some of the too rigid conceptions based on Shaffer's work that it is necessary to consider not merely the two known chemical factors, glucose versus fatty acids,

but also a third variable, the living organism which does not necessarily or invariably deal with the same food mixtures in the same way under all normal and pathological conditions.

In all of these investigations we have evidence that the symptoms of acidosis are due either to the pharmacological action of the products of disturbed oxidation, or to a deep-seated metabolic disturbance, rather than to the mere neutralization of the body's alkali by acids. In large part the substances occurring are not acids but ketones and related substances. On this point a very significant observation is mentioned by Talbot and his associates (49) as made by Parsons. He found that 20 per cent acetone injected into the rabbit in doses of from 1.5 to 4 cc. depending on the weight of the animal was sufficient to cause shock and often death. If 5 cc. of 20 per cent glucose were given intravenously it was generally sufficient to bring the rabbit out of shock almost immediately and to cause all signs of acetone intoxication to disappear. Somewhat similar observations on post-operative shock in patients are reported by Fisher and Snell (54).

Evidently the utilization of glucose in the tissues is a factor on a par with respiration and with the activity of the kidneys. These three functions interact in the physiological regulation of the acid-base balance of the blood.

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