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The Multiple Factor Theory of the Control of Respiratory Ventilation

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DURING THE PAST FIFTY YEARS a number of theories concerning the regulation of the respiratory minute-volume have been proposed. Although none of these theories has met with universal acceptance and none has been amenable to quantitative expression, it is of interest to review briefly their development as an introduction and background to the theory herein proposed.

The various theories proposed up to 1925 have one characteristic in common: they place respiratory ventilation under the control of a unique chemical agent whose effective concentration is located in the arterial blood. In the order of their proposal, these theories attribute the control of ventilation to the arterial oxygen tension, the arterial carbon dioxide tension, and the arterial hydrogen-ion concentration (*3, 10, 13*). There are, however, insurmountable objections to each of these theories. For example, the arterial pO_2 theory explains the respiratory response to anoxia, but affords no explanation of the respiratory responses to exercise, acidosis, alkalosis, or carbon dioxide inhalation, for there are no appropriate changes in the arterial pO_2 in any of these conditions. Similarly, the arterial pCO_2 theory explains the respiratory response to the inhalation of carbon dioxide, but provides no explanation for the changes in ventilation which accompany exercise, acidosis, alkalosis, or anoxia, for in all these conditions the alterations in arterial pCO_2 are in the wrong direction. Finally, the arterial H-ion theory explains the respiratory changes in metabolic acidosis and alkalosis, but fails to explain the responses in exercise, anoxia, or carbon dioxide inhalation; in anoxia the arterial H-ion concentration moves in the wrong direction, and in exercise and carbon dioxide inhalation the changes, although in the right direction, are wholly inadequate in degree. In summary, each of these theories merely restates the single phenomenon upon which it is based and fails completely to provide any understanding of other equally important phenomena.

The above conclusion, expressed forcefully and in some detail by Gesell in 1925 (*3*), provided the point of departure for new approaches to the problem of the regulation of respiration. Theoretically, there are at least three ways in which the difficulties of the above theories may be avoided.

(a) The principle that a unique chemical agent in the arterial blood is the only "true" stimulus to the respiratory center may be retained, but extended by assuming that final control of respiration depends upon variations in the irritability of the respiratory center towards this unique agent. Nielsen's (*13*) theory is an example of the application of this alternative.

(b) The principle may be retained that respiration is controlled by a unique chemical agent, but its effective concentration may be located elsewhere than in the arterial blood. Gesell's (*3*) theory is an example of the application of this alternative.

(c) The principle of a unique chemical agent may be rejected and replaced by the principle that a number of agents exert independent effects upon respiration and that the net ventilation under any given condition is determined by the sum of the partial effects of the separate agents. This alternative is the basis of the present multiple factory theory.

It is profitable to analyze examples of the first two alternatives. Nielsen's theory states (a) that carbon dioxide is the unique stimulus for the respiratory center, and (b) that the respiratory responses to exercise, acidosis, and anoxia are mediated by increased irritability of the respiratory center to the diminished CO_2 level. The first of these tenets is mistakenly based upon the experimental observation that CO_2 elicits a greater respiratory response per unit change in pH than other acids. The actual observation of responses to both stimuli denies Nielsen's conclusion of *unique* potency of one of them. The

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second tenet follows inevitably from the first, for, if CO_2 is the unique stimulus, and if, as Nielsen so nicely demonstrated, the CO_2 level is decreased in anoxia, acidosis, and exercise, one is compelled to interpret the accompanying respiratory responses as increased irritability to CO_2. In order to provide proof for such changes in irritability, he plotted the relationship between alveolar pCO_2 and ventilation in subjects breathing various percentages of carbon dioxide under conditions of rest, exercise, anoxia, and ammonium chloride acidosis. The resulting curves in the different conditions proved to be linear with the same slopes but with significantly different positions. The constant slopes reveal that a given increment in stimulus produces the same increment in response regardless of the conditions: this is evidence of unaltered irritability. The simple change in position suggests the influence of an additional factor, operating independently of CO_2. The two essential tenets of Nielsen's theory are therefore without experimental foundation. In spite of the fact that the theory considers carbon dioxide to be the only "true" stimulus to the respiratory center itself, it does introduce the notion that a number of factors are involved in the final control of respiration.

Gesell's original theory (*3*) stated that respiratory ventilation is controlled by the H-ion concentration within the respiratory center itself. This theory also preserved the principle of a unique respiratory stimulus and at the same time avoided the objections to the arterial H-ion theory. The improvement, however, is more apparent than real, for the H-ion concentration of the cells of the respiratory center is still beyond measurement. Nevertheless, the theory did emphasize the possible consequences of a lack of parallelism between arterial and cellular concentrations of stimulating agents, which may occur in transitory disequilibrium states, and in conditions of markedly altered blood flow.

With the discovery of the role of chemoreceptors in the carotid and aortic bodies, Gesell modified his theory to include indirect activation of the center through outlying sensory receptors (*4*). Furthermore, oxidation processes as well as H-ion concentrations within the cells are considered important in the activation of sensory receptors, both central and peripheral. This modified theory is no longer primarily a theory of the over-all regulation of respiration; rather, it is primarily a theory concerning the intracellular mechanisms by means of which certain agents, involved in the control of respiration, bring about stimulation or activation of receptor and effector cells. The two types of theory, however, are neither mutually exclusive nor competitive, but complementary.

The Multiple Factor Theory

The preceding theories for the most part may be called single factor theories, for they embody the principle of a unique stimulus for respiration or for the respiratory center. The fact that such theories have so consistently met with failure suggests a closer scrutiny of the principle of a unique stimulus. As a matter of fact, the poverty of direct evidence in favor of this principle stands in contrast to the wealth of homely evidence in favor of the opposite principle, that numerous factors influence respiration. The possibility that respiration is controlled by the integrated action of a number of factors has been repeatedly suggested, among others by Yandell (*12*) and Lawrence (*11*) Henderson and Bernthal (*1*) and more recently by Comroe (*2*). In fact, if Nielsen's theory (*13*) is divested of its postulates concerning a "true" stimulus and its site of action, it becomes a multiple factor theory. However, no one appears to have pursued this principle to its logical conclusions and to have attempted to apply it in a quantitative fashion. The present multiple factor theory is an attempt to do this.

In formulating the multiple factor theory it is important to distinguish clearly between the over-all regulation of respiration for homeostatic purposes and the intimate cellular mechanisms involved. The present theory is an attempt to describe quantitatively the integrated action of the various factors which control respiration, regardless of their sites of action or mechanisms. Like thermodynamics, it is concerned with the beginnings and ends of processes and not with the intervening steps, however important the latter may be from other standpoints. Since the multiple factor theory does not specify the site or mode of action of the various factors concerned, it will not stand or fall as a result of new developments along these lines. It should, in fact, serve as a useful guide in formulating and interpreting experiments designed to elucidate such mechanisms.

The multiple factor theory is based upon three fundamental principles, the first of which may now be stated explicitly. *The multiple factor principle states that a number of factors exert independent effects upon respiratory ventilation.*

The first step in the application of the multiple factor principle is to attempt to identify the various factors concerned. Since the administration of fixed acid, the inhalation of CO_2, and the withdrawal of O_2 result in increased ventilation, it is proper to consider these three chemical agents as possible factors. The recent demonstration that reflexes arising in exercising muscles bring about an increase in ventilation suggests an additional factor to be considered. The

list should also include pressoreceptor reflexes from the great arteries and great veins; thermoreceptor reflexes, presumably from the hypothalamus; and finally, pain reflexes and psychogenic reflexes. Of the above factors, the four most important ones, at present, appear to be three chemical agents and the muscle reflexes.

The second step in the application of the multiple factor principle is to decide at what point the concentrations of the three chemical agents are to be measured. Although ideally their concentrations should be measured in the respiratory center and the peripheral chemoreceptors where they exert their effects, this is not feasible. Venous blood levels are unsuitable because of the extreme variability in the composition of venous blood. Neither mixed venous blood nor blood from any accessible vein reliably reflects conditions both within the respiratory center and in outlying chemoreceptors. The only remaining possibility is arterial blood. There are also positive reasons which favor this choice. First, the chemoreceptors of the carotid and aortic bodies are believed to be exposed to arterial blood. In addition, parallelism between concentrations in arterial blood and in the respiratory center is promoted by the carefully regulated cerebral circulation. Finally, external respiration directly controls the gaseous composition of arterial blood. Accordingly, the most feasible approach is to correlate respiratory ventilation with the arterial concentration of the three chemical agents, bearing in mind the possibility that difficulties may arise in transitory unsteady states and in conditions of seriously altered blood flow.

It should be made clear that the multiple factor principle does not require that the partial effects of the separate agents be quantitatively fixed and invariable. The respiratory mechanism may, for example, be depressed by narcotic drugs and fail to exhibit a normal responsiveness to one or more of the respiratory factors. Such changes in sensitivity, however, should be demonstrated as an alteration in the slope of the stimulus-response curve of the partial factors in question.

A study of the behavior of the several agents selected above reveals that they are interrelated. Although, in accordance with the multiple factor principle, they may be considered to exert independent partial effects on ventilation, *they are not independent of one another.* It is well known, for example, that the arterial O_2 tension, CO_2 tension, and H-ion concentration are all elevated by the inhalation of CO_2 and depressed by the inhalation of air deficient in O_2, although in both instances ventilation is increased. It is known further that the increase in ventilation resulting from the administration of acidifying salts is accompanied by an increase in arterial O_2 tension and H-ion concentration and a fall in CO_2 tension. Finally, any reflex which increases ventilation without a corresponding increase in CO_2 production by the body as a whole will lead to acapnia and alkalemia. It is therefore apparent that the various respiratory agents influence one another to such an extent that a change in one agent alone rarely occurs either physiologically or pathologically. These observations provide the basis for the second principle of the multiple factor theory. *The interdependence principle states that a change in any one of the respiratory factors usually brings about changes in one or more of the other factors.*

If it is true that under most circumstances several factors are exerting independent but simultaneous influence on respiration, some method of combining the separate effects to represent the total effect must be adopted. The simplest device is to take the algebraic sum of the partial, or separate, effects to yield the total or combined effect. The necessity of specifying the algebraic sum arises from the fact that certain of the chemical agents are capable of inhibiting respiration, a situation represented by a negative partial effect. The total ventilation, of course, can never be negative, but the partial effect of an inhibitory agent may be considered negative. This flexibility and simplicity of the algebraic summation principle favors its adoption over that of a more complex device, such as taking the product of partial effects, which would imply synergistic action of the agents. The latter procedure should be avoided until actual evidence of synergism is encountered. This brings us to the third principle of the multiple factor theory. *The algebraic summation principle states that the actual ventilation is defined as the algebraic sum of the partial effects of the separate agents.*

It follows from the above principles that several types of effects on respiration must be carefully distinguished. A partial effect is the effect of a single agent when all other agents are kept constant. The actual ventilation rarely, if ever, represents a single partial effect. If all the partial factors are operating in the same direction, the actual ventilation represents an *additive* effect; if in opposite directions, a *difference* effect.

For the multiple factor theory to be successful as a theory it must be possible (a) to isolate and quantify the partial effects on ventilation of each of the important factors concerned, (b) to quantify the interrelationships between the various factors concerned, and (c) to demonstrate that algebraic summation of these partial effects does correctly predict the actual ventilation under various conditions.

During the past several years considerable progress

has been made in completing the above phases in the quantitative development of the theory. The first step consisted of the derivation on formal grounds of what has been called the alveolar equation (*5, 8*), which defines all possible relationships between alveolar (or arterial, since the two have been shown to be in equilibrium) O_2 and CO_2 tensions for any barometric pressure, alveolar RQ, and for any inspired gas mixture. This equation, like the others presented in Table 1, is fairly complex in its most general form, but happily reduces to much simpler forms for specific applications.

TABLE 1

EQUATIONS AND MATHEMATICAL SYMBOLS

1. The general alveolar equation (relationship between pO_2 and pCO_2):

$$pO_2 = \frac{(B\text{-}47\text{-}pCO_2)(RQ \cdot FO_2 + FCO_2) - pCO_2(1\text{-}FO_2(1\text{-}RQ))}{RQ + FCO_2(1\text{-}RQ)}$$

2. The general formal ventilation equation (relationships between actual ventilation and pCO_2):

$$VR = \frac{47\ MRR(RQ + FCO_2(1\text{-}RQ))}{pCO_2 - (B\text{-}47)\ FCO_2}$$

3. The general respiratory pathway equation (relationships between H-ion and pCO_2):

$$pCO_2 = \frac{H}{53.3}[(16 + 2.3\ O_{2_{150}})\ (\log H - 1.59) + BHCO_{3_{7.41}} + 0.375(O_{2_{150}} - O_2)]$$

4. The chemical ventilation equation (giving the sum of the partial effects of H-ion, pO_2, and pCO_2 on ventilation):

$$VR = 0.22H + 0.262\ pCO_2 - 18.0 + \frac{105}{10^{0.038pO_2}}$$

pO_2, pCO_2 = alveolar or arterial tensions of O_2 and CO_2, respectively
FO_2, FCO_2 = volumetric fractions of O_2 and CO_2 in dry inspired air, respectively
B = barometric pressure
RQ = alveolar respiratory quotient
VR = alveolar ventilation ratio (excluding dead space ventilation) expressed as the ratio of actual alveolar ventilation to resting alveolar ventilation
$VRpo_2$, $VRpco_2$, VR_H = alveolar ventilation ratio as it is influenced solely by the factor or factors identified in the subscript, all other factors remaining constant; partial ventilation ratio
VR_R = partial ventilation ratio due to action of muscle reflexes
H = H-ion concentration of arterial plasma; $pH = -\log H + 9$
$BHCO_{3_{7.41}}$ = bicarbonate content in vols. per cent of plasma from oxygenated blood at a pH of 7.41
O_2 = oxygen content of blood in vols. per cent
$O_{2_{150}}$ = oxygen capacity of blood in vols. per cent expressed as O_2 content of blood exposed to a pO_2 of about 150 mm. Hg
MRR = metabolic rate ratio, expressed as the ratio of the actual metabolic rate to the resting rate

The second step consisted of an analogous derivation on formal grounds of what has been termed the formal ventilation equation (*8*), which defines the possible relationships between the actual ventilation and the alveolar CO_2 tension for any condition of metabolic rate, alveolar RQ, and inspired gas mixtures.

The third step consisted of developing on empirical grounds what has been called the respiratory pathway equation (*9*), which defines the possible relationships between the arterial H-ion concentration and CO_2 tension, for any conditions of bicarbonate capacity, O_2 capacity, and arterial O_2 saturation.

The fourth and latest step to be completed consists of the isolation and quantification of the partial effects on ventilation of the three important chemical agents, H-ion, pCO_2, and pO_2. The partial effects of H-ion and pCO_2 were established empirically on the basis of extensive data available in the literature on the composition of blood in both respiratory and metabolic disturbance of acid-base balance. The partial effect of pO_2 was similarly established on the basis of extensive data (*6*), on the composition of alveolar air in decompression anoxia. These separate partial effects may be summed to yield what has been identified as the chemical ventilation equation (*9*).

The variables VR, H, and pO_2 may be eliminated from the chemical ventilation equation by substitution of the previous three equations, thereby providing a quantitative description of the behavior of respiratory ventilation under any conditions where the three chemical agents, operating normally, are controlling ventilation.

One of the major achievements of the present theory is that it resolves the most persistent and controversial question in the field of respiration: Should H-ion or CO_2 be considered the true respiratory stimulus? From the standpoint of the multiple factor theory this question should be framed as follows: To what extent does each of the two agents influence ventilation? Equation 4, which accurately describes the extensive experimental data, provides a quantitative answer to this question. If it were true that only one of the two agents is the true stimulus, the procedure used to establish Equation 4 would have betrayed the fact by emerging with a coefficient of zero for the inactive agent. Since neither of the coefficients is zero, it must be concluded that both agents independently affect respiration.

The combined action of the two agents, H-ion concentration and pCO_2, is illustrated in Table 2 by data which were calculated from the equations presented above and which accurately describe experimental findings. The first line of the table represents the normal resting condition, and the next two lines represent respiratory and metabolic acidosis, respectively. In all three conditions the metabolic rate ratio is unity; although there are changes in O_2 tension, the range covered is an inactive one for this agent. The inhalation of 5 per cent CO_2 elevates both the CO_2 tension and the H-ion concentration. Since the partial effects of both agents are stimulatory, a vigorous respiratory response occurs, amounting to a 268 per cent increase over the resting value. This marked response to the inhalation of CO_2 is, of course, well known. By contrast, an identical increase in H-ion concentration due to a metabolic acidosis, induced by NH_4Cl or any fixed acid, results in a comparatively feeble respiratory response, amounting to only 9 per cent. The reason for this becomes

apparent from an examination of the behavior of the CO_2 tension. The increase in ventilation mediated by the acidemia leads to hypocapnia, which exerts an inhibitory partial effect (indicated by a negative sign in Table 2), which nearly neutralizes the partial effect of the acidemia. It is important to note that the partial effect of the H-ion is identical in both types of acidosis, indicating unaltered sensitivity, but that in one type its action is assisted by the accompanying hypercapnia and in the other it is hindered by the accompanying hypocapnia.

TABLE 2

Condition	Arterial pO_2	Arterial pCO_2	Arterial reaction		Metabolic rate ratio	Partial increments				Total ventilation ratio
			H-ion	pH		$VRpo_2$	$VRpco_2$	VR_H	VR_R	
Resting	104.1	40	38.9	7.410	1.00	...	...	...	...	1.00
5% CO_2 inhalation ..	140.8	46.7	43.1	7.336	1.00	0.00	1.75	0.93	0.00	3.68
NH_4Cl acidosis	107.8	36.8	43.1	7.336	1.00	0.00	−0.84	0.93	0.00	1.09
Anoxia, 12,170 ft. ...	49.0	36.8	36.6	7.436	1.00	1.44	−0.84	−0.51	0.00	1.09
Passive exercise	121.1	28.6	30.7	7.516	1.00	0.00	−2.99	−1.81	5.20	1.40
Active exercise	104.1	40.0	38.9	7.410	6.20	0.00	0.00	0.00	5.20	6.20

Study of these data in Table 2 leads to the conviction that any attempt to explain them in terms of only one of the two arterial agents is doomed to failure. If, nevertheless, one insists upon the existence of a unique stimulus, be it H-ion or pCO_2, one is then compelled to assume fortuitous alterations in responsiveness to this stimulus. All these objectionable features are avoided simply and logically by the multiple factor approach.

The fourth line of Table 2 illustrates the combined action of all three chemical agents in anoxia resulting from exposure to altitude. At 12,170 feet, breathing atmospheric air, the reduced O_2 tension, operating through the chemoreceptors, increases the respiratory minute-volume. This respiratory response leads to hypocapnia, which in turn produces an alkalemia. The final increase in ventilation, as is well known, is relatively small, amounting in this example to only 9 per cent. The reason for this small response is that the partial effects of both the hypocapnia and alkalemia are inhibitory and nearly neutralize the partial effect of the anoxic stimulus.

The lack of a satisfactory explanation of the intense respiratory response to exercise has been a serious deficiency of previous theories. Although analysis of this problem in terms of the multiple factor theory has not been completed, the usefulness of this approach may be indicated by the following preliminary analysis. It has recently been demonstrated that a purely reflex respiratory response occurs in passive exercise (*2*). Since the response, however, is so small in comparison to the response to active exercise, it has been considered to play a negligible role in active exercise. That this conclusion is wholly unjustified is indicated by the calculations presented in the last two lines of Table 2. It has been reported (*2*) that passive exercise of one leg in human subjects produces an average increase in ventilation of 40 per cent. If it can be assumed that the passive nature of the exercise prevents any change in metabolic rate, it can be calculated that a considerable hypocapnia and alkalemia must have resulted. Since the reflex increased ventilation against the marked inhibitory action of these changes, it must have been quite powerful—in fact, so powerful that, acting alone, it should increase ventilation by 520 per cent. When this reflex is operating under more normal conditions of active exercise, it should not meet with opposition, for the metabolic rate and CO_2 production should be increased. The last line of Table 2 shows that, granted a reflex of this same intensity in active exercise, it should be able to handle a 520 per cent increase in metabolism without any disturbances in gas transport, or disturbance in the levels of gas tensions or pH. Contrary to the original conclusion, this analysis implies that the muscle reflexes may play a major role in mediating the respiratory response to exercise. It further implies that the chemical agents play a minor role in this situation, an implication which certainly is in harmony with experimental observations on the behavior of these agents in exercise. It may be tentatively concluded that in exercise the chemical agents carried by the blood stream provide (a) a fine adjustment of ventilation, automatically brought into play when the reflex response is not otherwise exactly commensurate with the increased requirements for gas transport, and (b) the adjustment required as compensation for the metabolic acidosis of severe exercise.

The multiple factor theory has already proved its usefulness in the analysis of respiratory problems in aviation. It provides accurate estimates of O_2 requirements at various altitudes (*5*), of equivalent altitudes breathing various percentages of O_2 (*7*), and provides a basis for determining the effects of adding CO_2 to various gas mixtures at altitude (*8*). It has also afforded a quantitative description and explana-

tion of the mean pathways for disturbances of acid-base balance (*9*). It promises to reveal additional insight into acclimatization to altitude and into the various stages of compensation to acid-base balance disturbances.

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Technical Papers

Radioactivation of Colloidal Gamma Ferric Oxide

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Welo and Baudisch (*7*) were the first conclusively to establish that ferric oxide—Fe_2O_3—exists in both a cubic and a rhombohedral form. The cubic form, γ ferric oxide, is the labile one and ages slowly, under loss of energy, into the stable rhombohedral form, the common α Fe_2O_3 or hematite. The cubic or spinel type, γ Fe_2O_3, possesses magnetic properties similar to, but feebler than, metallic iron and, in addition, a remarkable number of catalytic and biocatalytic qualities. The rhombohedral, α Fe_2O_3, which is not magnetic, is also active in a biocatalytic manner but to a lesser degree than the cubic form.

It is obvious that the difference in physical behavior of the two chemically identical modifications of iron oxide must be attributed to the difference in their crystal structure. Many investigators have studied the crystal structure of these iron oxides (*6*). The result of these investigations was the discovery that the lattice in the structure of γ Fe_2O_3 is incomplete. The lattice of γ Fe_2O_3 contains so-called "interstitial spaces" (atomic holes) which, in the more stable lattice of α Fe_2O_3, are filled up by ferric ions. The elemental crystal of γ Fe_2O_3 contains an average of $21\frac{1}{3}$ ferric ions compared to an average of 24 found in the crystal of α Fe_2O_3. This was ascertained mainly by a number of experiments dealing with the diffusion of liquids and gases in these crystals. It was found, for instance, that radium emanation diffuses freely through the "atomic holes" in γ Fe_2O_3 crystals, while α Fe_2O_3 is almost impenetrable to this emanation; in this case, the "atomic holes" are blocked at room temperature. The diameter of these "atomic holes" or channels in γ Fe_2O_3 ranges between 5.2 A. and 7.5 A., as the benzene molecule (diameter, 5.2 A.) may penetrate the crystal, but the xylene molecule (diameter, 7.5 A.) is unable to do so.

The fact that the cubic, ferromagnetic iron oxide possesses these "atomic holes" is of great significance, since within the crystal a secondary structure, or "inner surface" is formed. The comparatively great surface of this crystal is mainly responsible for the high catalytic reactivity of the material. Also, the "atomic holes" create electric disturbances within the crystal which may also influence the reactivity of the compound.

The properties of γ Fe_2O_3 remain unchanged when put into a colloidal state (*1*), and it is in this form that it is especially suitable for certain biological purposes. Colloidal solutions were prepared with a colloid mill, using as a carrying medium dextrin, olive oil, and gum arabic; the particle size obtained was 10^{-5} cm. or smaller.

Gamma ferric oxide in colloidal form may be injected directly into the blood stream. Peyton and Beard (*5*) found that the colloidal particles of γ Fe_2O_3 are taken out of the blood stream by the reticulo-endothelial cells, which are phagocytic to foreign materials of this type. These authors first isolated Kupffer's cells (reticulo-endothelial cells of the liver) by passing a sodium chloride solution through the liver and then using an electromagnet to separate the cells, the latter having been transformed into living magnets by the absorption of colloidal γ Fe_2O_3 particles. These reticulo-endothelial cells are distributed throughout the body, but are most abundant in the liver, spleen, and bone marrow. They