from, and an important part of, the science of normal behavior-experience. If the various divisions of biology, functional and structural, are entitled to acceptance as natural sciences of measurement and prediction, then, from the facts provided by these exhibits, we must grant that psychology actually exists as science. Moreover, whether or not we chance to be medically trained or interested especially in psychopathology, we psychologists and psychobiologists are working in the spirit, with the objectives, and, in principle, with the methodologies of the other physical and biological natural sciences.

Obviously, my disagreement with the authors of *The Peckham experiment* is absolute. Nevertheless, as scientists we all are committed to strive for progress, and most of us recognize that what today appears impossible may be achieved tomorrow. I should like to suggest, if it be not presumptuous, that either the Crown or the Prime Minister of Great Britain appoint a commission of experts to visit the United States of America expressly to inquire into the existence and status of the "impossible" sciences of human behavior-experience, social organization, and institutions, and to report authoritatively and informatively to the people of Great Britain. Belief and action should not depend upon the assertions of the editors of *Endeavour*, of the authors of *The Peckham experiment*, or of an American scientist who refuses to admit that it is impossible for any one person to be physicist, biologist, sociologist, all in one, and to seek always to advance knowledge and human welfare as *scientist*, sometimes as *specialist*.

On the Multiple Factor Theory of Respiratory Control as Outlined by Gray

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A RECENT ARTICLE ON A MULTIPLE factor theory of control of respiratory ventilation (*4*) carries certain wide implications for which the author did not present the necessary substantiating data. Furthermore, many of the statements seem highly questionable, if not erroneous; e.g. a categorical statement that all preceding theories of control have "consistently met with failure" is presented without evidence.

Gray states that Gesell's theory "avoided the objections to the arterial H-ion theory" and that "the improvement, however, is more apparent than real, for the H-ion concentration of the cells of the respiratory center is still beyond measurement." If this statement means that Gesell's theory is difficult to handle quantitatively, we must agree. Otherwise, the meaning is not clear.

There is a considerable body of evidence that respiratory center acidity and chemoceptor acidity run parallel to respiratory minute volume. Cerebrospinal fluid acidity (*2*) offers a first approximation of central nervous system acidity. These approximations have been abundantly supported by observations on venous blood acidity. Present information on central nervous system chemistry and metabolism permits related deductions concerning the acidity of the center (*7*). Whatever method is employed to appraise intracellular acidity of the respiratory center and chemoceptors, the premise that intracellular acidity plays an important role in the control of respiratory ventilation is supported (*2*).

Gray seems to have accepted the views of Gesell on this major issue of intracellular acidity, for he writes as follows:

> 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.

This is a point which cannot be passed over lightly, for if one fact is established with reasonable certainty, it is the lack of correspondence between the concentration of H-ions and of CO_2 in the arterial blood and the volume of respiratory ventilation. Of all the points of concentration, arterial blood is the least informative. Yet Gray states that "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 is a well-known fact that venous blood is usually more acid than arterial blood and that the increase in

H-ion concentration occurring as it passes through the tissue is due to the addition of acid metabolites to the blood by the tissues. Gesell and his co-workers have clearly shown that hemorrhage increases the difference in H-ion concentration of venous and arterial blood. Despite a decrease of H-ion concentration of arterial blood of pH 0.1 or more, due to augmented ventilation of the blood in the lungs, both the venous blood and the cerebrospinal fluid turn more acid than normal as a result of hemorrhage (*6*). Such exaggeration of differences in H-ion concentration of arterial and venous blood is not so transitory as Gray seems to imply and throws considerable light on the mechanisms of respiratory control. Yet Gray is of the opinion that "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." It is one matter to use the H-ion concentration of the arterial blood to meet the convenience of the investigator. It is another matter, as Gray himself has pointed out, to select the site of concentration which throws most light on the mechanisms involved in the control of respiratory ventilation. If one uses the H-ion concentration of the arterial blood because it reflects the acidity of the respiratory center, as Gray in one place implies, it is somewhat illogical at another place in the line of reasoning to consider the H-ion concentrations of the arterial blood as the stimulating agent. Gray's dilemma increases on realization that the volume of pulmonary ventilation varies inversely as the H-ion concentration of the arterial blood in a number of important types of hyperpnea, and in some of these the carbon-dioxide pressure is low and the oxygen pressure high.

Gray's Chemical Ventilation Equation

The chemical ventilation equation as given by Gray (*4*) is:

$$VR = 0.22H + 0.263pCO_2 - 18.0 + \frac{105}{10^{0.038pO_2}}.$$

Such an equation is a device to predict the magnitude of the ventilation when H, pCO_2, and pO_2 are known. But we doubt very much, unless independent substantiating evidence is presented, that the equation can be used to establish causal relationships or provide information on the mechanisms by which H, pCO_2, and pO_2 are related. While the algebraic device is simple to handle from the standpoint of the mechanical manipulations of the data, it is not necessarily better than other devices, and other devices should be avoided only after proof is presented that they are less reliable than the algebraic device. A rigid mathematical analysis will also give a product which can be used to predict respiratory volume. The problem is which prediction will give the smallest relative or absolute error. The equation to be favored is the one giving the most accurate prediction. Among the equations deserving investigation are (1) and (2), formulated by Krueger.

$$(1) \qquad y = ax^by^cz^d \text{ or } \operatorname{Log} y = \operatorname{Log} a + b \operatorname{Log} x + c \operatorname{Log} y + d \operatorname{Log} z$$

$$(2) \qquad y = ab^xc^yd^z \text{ or } \operatorname{Log} y = \operatorname{Log} a + x \operatorname{Log} b + y \operatorname{Log} c + z \operatorname{Log} d$$

$$\text{or } \operatorname{Log} y = A + Bx + Cy + Dz.$$

None of the equations, including Gray's, has any value unless the probable or standard error of the prediction is also known. One can predict the magnitude of ventilation even without knowing what is meant by volume of respiration; but here the probable error of the guess is exceedingly great. A prediction is valueless unless one can associate with it a standard error and thus provide some concept of the validity of the prediction. Gray has neglected to include the standard error with his equation. Further, Gray's equation would be of value only where it can validly be used. Gray defines the realm of validity as any condition where H, pCO_2, and pO_2 of the arterial blood, operating normally, are controlling respiration. But what are the criteria that only these three factors and not others, such as muscle and other reflexes, pain, body temperature, or metabolism, are influencing respiration? When do these factors operate *normally*? The validity of a predicting equation also depends upon the source and quantity of data from which it is derived, and Gray has not published this information.

As a reason for avoiding a product of H, pCO_2, and pO_2 for the prediction of the magnitude of ventilation, Gray has said that taking the product of partial effects implies synergistic action, and that such a procedure should be avoided until actual evidence of synergism is encountered. If this were true, his own equation should also be avoided, because that equation implies synergism. Synergism usually is defined as a working in the same direction. In his equation the H, pCO_2, and pO_2 components are always positive and hence always *arithmetically* as well as *algebraically additive*. Since the three components always act in the same direction, they are, by definition, synergistic. If one is to consider Gray's equation as a functional mathematical equation rather than a prediction equation, one wonders how the constant -18.0 is to be interpreted. The constant can be separated into three components, each to be associated with the H, CO_2, or O_2 component, and thus provide the possibility

for negative partial effects related to the H, CO_2, and O_2 components. Yet one must keep in mind that (1) the arterial hydrogen ions and carbon dioxide are presumed to stimulate in proportion to their concentrations; (2) the oxygen always gives a positive component which is less, the higher the oxygen concentration; and (3) the effects of the H, pCO_2, and pO_2 components are always positive, no matter what negative constant is associated with them. This difficulty could be eliminated by establishing arbitrary zero lines for H, CO_2, and pO_2 and using a more complex function of these components; but Gray has neglected to do this. Hence, if one accepts his formula as a functional mathematical equation, one must conclude that the effects of H, O_2, and CO_2 are arithmetically additive (always positive) and hence synergistic, that these factors operate on a center whose nonstimulated condition represents a value of -18.0, and that the sum of the O_2, CO_2, and H components must reach 18.0 before ventilation occurs. A more logical attitude is to treat Gray's equation as a pure prediction equation. If we know something of the H-ion concentration, the arterial O_2, and the arterial CO_2, we can make a prediction regarding the magnitude of the ventilation.

Beyond presenting his prediction equation, Gray's only suggestion, offered without proof, is that certain factors may act independently. Gray holds that "if it were true that only one of the two agents [CO_2 or H-ion concentration] is the true stimulus, the procedure used to establish the equation [4] would have betrayed the fact by emerging with a coefficient of zero for the inactive agent." In order to reduce this argument to an absurdity, an equation will now be derived from Gray's equation where the coefficient of CO_2 is zero; then, if we were willing to follow the logic of Gray, we could conclude that it was not the CO_2 and H-ions of the arterial blood, but rather the bicarbonate ions and the H-ions which were the true respiratory stimuli. From the law of chemical equilibrium,

(3) $[H^+] \times [HCO_3^-] = K_1 \times [H_2CO_3] = K_2 \times pCO_2$ (*5*).

Hence,

(4) $pCO_2 = [H^+] \times [HCO_3^-] K_3$,

and substitution in Gray's equation yields Equation 5.

$$(5) \qquad VR = 0.22H + 0.263 \times K_3 \times [H^+] \times [HCO_3^-] - 18.0 + \frac{105}{10^{0.038pO_2}}.$$

In Equation 5 the coefficient of CO_2 is zero. Because we do not attach any functional significance to either Gray's equation or Equation 5, we continue to believe that the blood carbon dioxide *influences* respiration.

Gray uses his equation to predict the relationships in passive muscular exercise. He assumes that the passive nature of the exercise prevents any change in metabolic rate. The metabolism during passive exercise is readily amenable to evaluation and should be evaluated experimentally before assuming that metabolism will not be changed. Since the experiments of Cohnheim on *Sipunculus* and of Cohnheim and Von Uexküll on the leech showed that the energy consumption is greater in these animals when loaded than when unloaded (*1*, p. 538), it is possible that the changes in tension and length may produce an increase in metabolism during passive exercise. Hence, one cannot as yet take at face value the calculation which associates no change in metabolism with a decrease from 40 to 29 mm. Hg in the blood carbon-dioxide pressure, a change in pH from 7.41 to 7.52, and an increase of 40 per cent in ventilation during passive exercise.

Comments on Nielsen's Theory

Nielsen (*9*) views CO_2 as the unique stimulus for respiration and assumes that the irritability of the respiratory center to this stimulus is variable. CO_2 produces a greater increase in respiration per unit change in the pH of the arterial blood than is produced by other acids. Gray categorically claims that a unique potency of CO_2 is denied by the fact that both acid and CO_2 increase respiration. He seems to overlook the fact that injection of acid causes an increase in CO_2 and that CO_2 could be the effective factor in producing an increase in respiration. We would like to comment further that there is some similarity between Nielsen's theory, invoking the unique stimulus of CO_2 acting upon a center whose irritability varies, and that of Gesell, which relates the changes in respiration to tissue acidity and to the acetylcholine concentration at certain key points. If the irritability in Nielsen's theory were defined in terms of bicarbonate and acetylcholine content, the two theories would be very closely related. In that acetylcholine and acidity are more clearly defined entities than irritability, it is easier to think in terms of Gesell's theory than of Nielsen's. The latter theory is a reflection of early similar statements by Loewi (*8*) and others.

Classification of Theories of Respiratory Control

Careful over-all consideration of the adjustment of breathing leads to the inescapable realization that a very large number of factors—many more than are usually considered—must participate in the control of respiratory ventilation. Gesell (*2*) and Gesell and Hansen (*3*) have emphasized this point in their papers. If it is true, as these authors have suggested, that the electrogenic properties of acetylcholine may provide the activating forces of the respiratory center, the heterogeneous factors contributing to the control of breathing become

resolvable into a final common factor, namely, concentration of free acetylcholine in the respiratory center. Synaptic bombardment of the respiratory center by impulses originating in chemoceptor endings, in pain endings, in proprioceptive endings of the lungs, of respiratory muscles and locomotor muscles, and impulses originating in the higher centers should lead to liberation of acetylcholine in the center. Increased acidity of the center resulting from any of many possible causes should, by its anticholinesterase activity, potentiate the effects of prevailing bombardment of the center. Theoretically, an increase of H-ion concentration and of CO_2 concentration and a decrease of O_2 concentration of the arterial blood should increase the acidity of the tissue. Thus, these three factors, which Gray has emphasized, are theoretically resolvable into the single factor, tissue cH. The view that both increased bombardment of the center and increased intracellular cH lead to increased concentration of acetylcholine offers an extremely simple theory for explaining respiratory ventilation. Because a host of heterogeneous factors must be theoretically resolvable into a final common factor such as neurocellular electrotonic currents, however, is no reason for identifying Gesell's theory as a single factor theory. If there be need of classifying theories of respiratory control into single and multiple factor theories, Gesell's theory should be included with the latter. A quantitative elaboration of all the factors to which Gesell has called attention is a more difficult problem. Although much quantitative data concerning the regulation of respiration are available, any inclusive formulation which would account for the many factors and their interactions becomes extremely cumbersome. On the other hand, necessary simplification renders any such formulation hypothetical.

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Reply to Krueger's Criticism of the Multiple Factor Theory

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A THUMBNAIL SKETCH OF RESPIRATORY theories will be of assistance to the reader whose only recent information on the subject consists of Krueger's article. Early theories which postulated a *single arterial stimulus* for respiration have long been realized to be incompatible with experimental observation. Later theories, which have added a second postulate, that a number of factors influence the *sensitivity* of the respiratory center to the unique arterial stimulus, are also at variance with experimental observation. A third type of theory, such as Gesell's *original* theory, which postulated that ventilation is controlled by a single *immeasurable* stimulus, namely, the intracellular pH of the respiratory center, is impossible to quantitate. In order to avoid these difficulties, the multiple factor theory postulates that a *number of stimuli* exert individual effects on ventilation; that the levels or concentrations of these stimuli are frequently influenced by one another; and that, as a result, the actual ventilation represents the algebraic sum of the partial effects of the separate stimuli. The logical implications of these postulates have been worked out in detail and given quantitative mathematical expression; they have been applied to very extensive and well-known experimental data and found to give excellent agreement and to provide a greatly enhanced understanding of the control of respiration. All these details have been presented in a series of seven wartime reports (*1–5*), totaling some 220 pages, released from the AAF School of Aviation Medicine. The *Science* article (*6*) which Krueger criticizes constituted a brief summary of the principles and general nature of the theory.

The multiple factor theory, like any other theory in science, can be legitimately criticized on the grounds that it fails to correspond to experimental observation, or that it is logically inconsistent with itself, or that it is not verifiable. Few of Krueger's criticisms fall into any of these categories, as may be seen from the following criticisms and answers:

(1) Krueger's opening sentence claims that necessary substantiating data were not presented. This accusation is made a number of times. The facts are that extensive substantiating data were presented in the wartime reports (*1–3*) (available on request) given as references in the *Science* article, but which Krueger has ignored. More