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

detailed evidence of the failure of preceding theories is also included in these reports.

(2) In his second paragraph Krueger states that the only interpretation he can make of my criticism of Gesell's (original) theory is that it is difficult to handle quantitatively. This interpretation is correct. Is it an error to consider unsuccessful a theory which is not amenable to quantitative expression, but which, nevertheless, treats of quantitative events? Krueger implies that my criticism of Gesell's *original* theory was leveled at Gesell's *modern* theory. In fact, the main theme of Krueger's paper is the defense of Gesell's modern views against my supposed attack. This defensive effort would have been more appropriate had there been any actual attack. I can do no better than quote my original words (*6*):

> This modified theory [Gesell's] is no longer primarily a theory of the over-all regulation of respiration [in contrast to the multiple factor theory]; 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.... It is important to distinguish clearly between the over-all regulation of respiration for homeostatic purposes and the intimate cellular mechanisms involved.... Like thermodynamics, it [the multiple factor theory] is concerned with the beginnings and ends of processes and not with intervening steps, however important the latter may be from other standpoints.

(3) Krueger registers numerous objections to the use of arterial blood levels of the chemical stimuli.

(a) One objection is based on the claim that arterial levels are least informative because it has been established that they do not correlate with ventilation. What had already been established was that no *single* arterial agent correlates with ventilation; what I have established on the basis of experimental data is that *multiple correlation* between ventilation and the *several* arterial agents is quite good.

(b) Another objection is based on the allegation that arterial levels were chosen "to meet the convenience of the investigator" instead of to "throw more light on the mechanisms involved in the control of respiration." Arterial levels were admittedly selected because they are more feasible to measure; my preference for accomplishing the feasible rather than speculating on the infeasible seems not to be shared by Krueger. Having selected a feasible procedure, it thereby became possible to discover that it threw more light on the control of respiration. The justification for this selection consists of the fact that it led to the discovery of a multiple correlation between arterial levels and ventilation.

(c) Krueger accuses me of inconsistency in considering the arterial H-ion to *reflect* the acidity in the respiratory center in one place and in another to *be* the respiratory stimulus itself. The fact is that I did and do consider the arterial pH in many important conditions to be a measurable index of the effective pH, whatever the value of the latter may be and regardless of its site of action.

(d) Krueger implies that I have not considered situations in which arterial and cellular pH's may be dissociated. The truth is that I have considered some of these conditions in considerable detail (*2*, *4*).

(4) Krueger also devotes a number of pages to criticism of the chemical ventilation equation.

(a) Doubts are expressed that it "can be used to establish causal relationships." The fact is that no equation ever established causal relationships, and this one was not intended to do so. If one must think in anthropomorphic terms, it might be pointed out that the chemical ventilation equation describes the "causal" effect of arterial pCO_2 on ventilation, and the formal ventilation equation describes the "causal" effect of ventilation on the arterial pCO_2, thus for the first time explicitly clarifying certain confusing "causal" relationships in respiration.

(b) Doubts are also expressed that the equation can "provide information on the mechanisms by which H, pCO_2, and pO_2 are related." These doubts are well founded; the equation does not and was not intended to do this. A group of three other equations were provided for this purpose.

(c) Krueger objects to the chemical ventilation equation because other "equations deserving investigation" were not explored. As a matter of fact, the chemical ventilation equation represents the only one among a number explored which was found to describe the experimental data. It must be confessed, however, that no attempts were made to fit exponential or logarithmic equations to linear data!

(d) Krueger also objects to the algebraic summation device on the grounds that simple arithmetic summation is all that is required. The thread of the argument at this point becomes incoherent. He says that the equation "provides the possibility for negative partial effects" and, further on, that from the equation "one must conclude that the effects of H, O_2, and CO_2 are arithmetically additive (always positive)." The first of these contradictory statements is the correct one. The confusion finally culminates in Krueger's explicitly redefining "synergistic" as synonymous with "additive," thereby enabling the conclusion to be drawn that my expressed preference for additive effects (my definition) is really a preference for synergistic effects (his definition) when I profess to shun synergistic effects (my definition).

(e) Krueger undertakes to demonstrate the "absurdity" of my statement, viz., that the procedure used to establish the chemical ventilation equation would have yielded a zero coefficient if either H-ions or pCO_2 *alone*

were influencing ventilation. It is pertinent to remark that the procedure employed was not described in the *Science* report which Krueger read. His "demonstration" consists of replacing $BHCO_3$ for pCO_2 in the equation, leaving *two* essential variables still present, and thus confirming my statement that one variable alone does not account for the experimental data.

(5) Krueger takes exception to my analysis of the respiratory response to exercise because I assumed that metabolism is not increased by passive exercise. This analysis was adequately labeled as incomplete and preliminary; the tentative nature of the *quantitative* values was indicated. The *qualitative* validity of the conclusions requires only that passive exercise produce less increase in metabolism than in ventilation in comparison with active exercise.

(6) It is claimed that in referring to Nielsen's theory I state "categorically" that a unique potency of CO_2 is denied by the fact that Nielsen obtained a response to both acid and CO_2. My statement was that the occurrence of responses to both agents denied the conclusion Nielsen drew from them, namely, that only *one* was a potent stimulus. Krueger further states that I "overlooked" the fact that the injection of acid causes hypercapnia, which could be responsible for the respiratory response to the acid. The truth is that I have analyzed the acute responses to injected acid in detail (*4*). Unfortunately, Krueger seems to have "overlooked" the fact that Nielsen did *not* inject acid, but fed NH_4Cl and that he observed *acapnia* (as have all others) and not hypercapnia.

The title I selected for my theory has turned out to be an unfortunate one, in that it does not adequately distinguish it from other theories. The consequences have been that the theory is superficially judged to be no different from others, since its title can be appropriately applied to others. Many theories have included multiple *factors* presumed to operate by controlling the concentration of a unique stimulus or by controlling the sensitivity of the respiratory center to a unique stimulus. The multiple factor theory differs from these in that it postulates multiple *stimuli* exerting individual or partial effects. Gesell's and Nielsen's theories, therefore, are appropriately classified as multiple factor theories, and mine might better have been called the multiple stimulus theory.

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Chemical Research Conferences, AAAS, 1947:

Colby Junior College, New London, New Hampshire, June 16–August 22

W. George Parks, *Director,*
Rhode Island State College, Kingston

INFORMATION ON THE CHEMICAL RESEARCH Conferences for 1947 with respect to location, purpose, and registration was published in the preliminary announcement in *Science* (March 14, 1947).

Requests for attendance at the Conferences or for any additional information should be addressed to W. George Parks, Department of Chemistry, Rhode Island State College, Kingston, Rhode Island. From June 15 to August 20, 1947, mail should be addressed to Colby Junior College, New London, New Hampshire.

The final program follows:

ORGANIC HIGH POLYMERS

C. C. Price, Chairman; W. O. Baker, Vice-Chairman

June 16 C. S. Marvel, "New Monomers for Synthetic Rubber"; R. L. Frank and Norman Rabjohn, "Structure of Synthetic Rubbers."

June 17 G. S. Whitby, "Proliferous Polymerization of Butadienes"; John Rehner, Jr., "The Polyisobutylene Reaction."

June 18 A. J. Warner, "New Polymers"; H. Mark, "Cyclo-octotetraene."

June 19 A. V. Tobolsky, "Aging and Degradation of Polymers"; E. H. Farmer, "Thermally-promoted Olefinic Reactivity and Polymerization."

June 20 M. G. Evans, The University, Leeds (tentative).

CATALYSIS

Walter G. Frankenburg, Chairman; H. S. Taylor, Vice-Chairman

June 23 Aristid V. Grosse, "Concept of Catalytic Chemistry"; H. S. Taylor, "New Data on the Heterogeneity of Catalytic Surfaces."

June 24 James B. Sumner, "Chemical Nature of Biocatalysts; Problems Concerned With the Isolation of Enzymes"; Paul H. Emmett, "Adsorption of Carbon Monoxide and Hydrogen on Carbided Iron Catalysts."