Humoral Regulation of Breathing

The concepts presented by Armstrong *et al.* in their article "The humoral regulation of breathing" (*1*) should not be allowed to go unchallenged. In ten pages of computation and speculation the authors claim evidence that control of respiration is mediated via peripheral chemoreceptors sensitive to humoral changes in both arterial and venous blood. The venous receptors are supposed to be located in the pulmonary artery. The respiratory center is viewed by the authors as merely a "computing mechanism" to respond to afferent neural stimulation.

It is likely that the authors may find some disagreement with their contention that the brain serves only as a computer. The specific existence of osmoreceptors and thermal receptors has long been known (*2*). That the respiratory center may respond directly to chemical stimulation has also been shown. Comroe in 1943 demonstrated a ventilatory response to injection of CO_2-bicarbonate mixtures directly into certain localized areas of the brain stem of the cat (*3*). Loeschke more recently has infused solutions into the cerebrospinal fluid to demonstrate also a central chemoreceptor response (*4*). To divorce the brain from its time-honored role of sensitivity to humoral changes and relegate it to the chore of computation seems scarcely justified.

The correlation between the magnitude of ventilation and venous blood P_{CO_2} and H^+ under a variety of conditions (for example, CO_2 breathing and exercise) is well known. The authors' extensive mathematical gymnastics do nothing to pinpoint the site of action of the chemical stimuli. One cannot know whether venous P_{CO_2} and H^+ serve as stimuli to an as yet unlocated pulmonary artery chemoreceptor, or whether these chemical parameters only reflect the actual operating conditions within the chemosensitive cells of the respiratory center. It is not surprising that a crude mathematical correlation between ventilatory response and H^+-P_{CO_2} of mixed venous blood can be demonstrated. If it were possible to isolate the venous outflow from the respiratory center itself, a far better mathematical fit might well be obtained.

Perhaps it would be more appropriate to devote future efforts to demonstration of the physiologic existence of these elusive venous chemoreceptors, before assigning to them such an all-important role in the regulation of respiration.

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We agree with the opening statement in the above letter—the concepts in our article should not go unchallenged. Several aspects of the presentation are admittedly controversial and, therefore, subject to challenge.

The paper was prepared with two objectives in mind: first, and primarily, to discuss some consequences of postulating a mixed venous chemoreceptor with functions similar to those of known arterial chemoreceptors. Having done this, such a variety of respiratory responses could be accounted for that several obvious questions arose: What *is*

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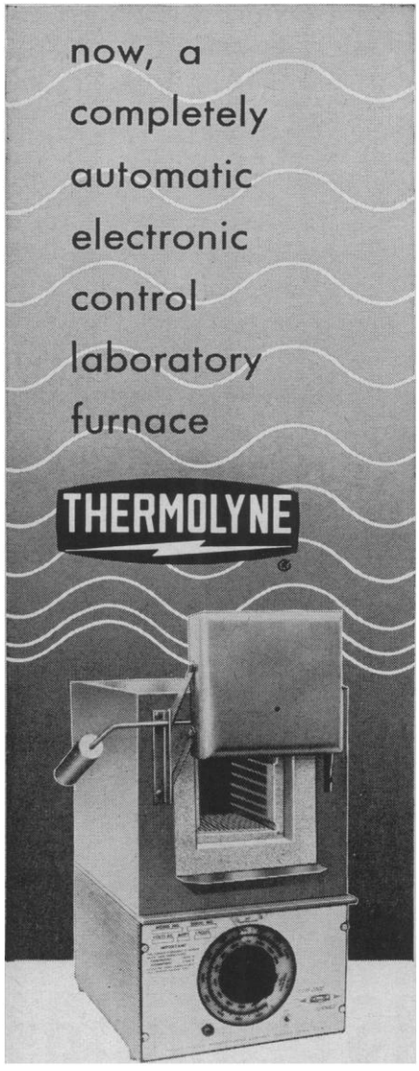

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the function of the respiratory center; is it analogous to a computer, or to a transducer, or does it have both sensory and integrative functions? Does arterial blood contain enough "information" for the body to regulate breathing and maintain arterial homeostasis? Are the efforts to wring out of arterial blood the data necessary to account for the hyperpnea of exercise a manifestation of laudable perseverance, or do these efforts represent a reluctance to abandon familiar concepts?

The second objective, then, was to raise these questions in public. Although we cannot answer these questions, in approaching them it seems helpful to put classic teaching into syllogistic form:

1) There is a respiratory center.

2) A respiratory response regularly follows the administration of many substances—inhalation of CO_2, intravenous injection of acids, and so forth. (At this point haven't many of us made the following inference that over the years has acquired the weight of a deduction?)

3) Therefore, the observed respiratory response is produced because the administered agent has stimulated the respiratory center.

In another argument, the second premise becomes:

2) A positive respiratory response often follows the introduction of certain substances into the respiratory center (or the cerebral spaces).

While it certainly follows that the central nervous system is chemosensitive to such substances, this is no proof that there is a chemoreceptor in the brain; it may only mean that the integrative action of the central nervous system has been disturbed by the procedure.

An interesting point is raised in Roos and Hornbein's third paragraph, where they imply that "operating conditions within the chemosensitive cells of the respiratory center" and "the composition of venous outflow from the respiratory center" are sufficiently altered by exercise to account for the observed hyperpnea. This may be, but we are unaware of supporting data. If the composition of blood draining the respiratory center can be assumed to parallel that of internal jugular blood, the possibility seems unlikely. In contrast to the venous drainage from most regions, the composition of internal jugular blood remains essentially stable at rest and during even severe exercise [J. H. Mitchell *et al.*, *J. Clin. Invest.* **37**, 1693 (1958)].

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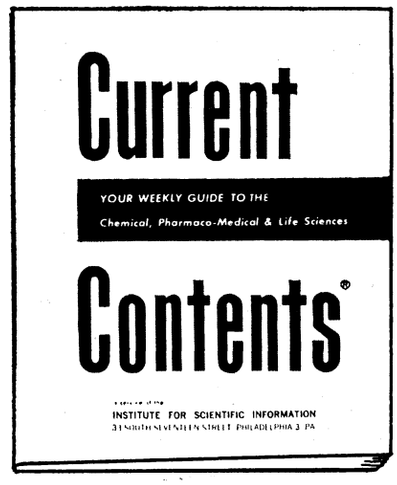

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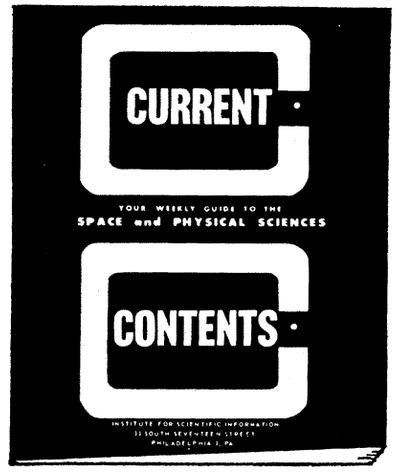

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For the convenience of readers who do not have our original article at hand, we point out that the respiratory center was not characterized as "merely" a computer, and it was not "relegated to the chore of computation." It was described as analogous to a computer; we assumed that readers would share our respect for computations done by the central nervous system. Neither was the mixed venous chemoreceptor mechanism "supposed to be located in the pulmonary artery." The glomus pulmonale (which is in the pulmonary artery) was described to show that the anatomic structure necessary for the concept exists; whether or not it is a chemoreceptor, we do not know. The equations and numbers in our article were derived by operations of arithmetic and elementary algebra, not from "extensive mathematical gymnastics." Nor were they intended to "pinpoint" the site of any action. The most extensively discussed equation (Equation 5) was used, primarily, to summarize much of our concept quantitatively—much as the second paragraph of the "Summary" does with words.

Finally, we are aware of the consequences of iconoclasm and those that often attend discussion of bits of indirect evidence which, when taken together, trend to support an unproved hypothesis. Since existing theory of respiratory regulation seems to have reached an impasse, a new approach, however challenging it may be, seemed, and continues to seem, appropriate.

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Academic Biology in Europe

William V. Consolazio's article on the "Dilemma of academic biology in Europe" [*Science* **133**, 1892 (1961)] painted a picture in the biological field which is in sharp contrast to what I had observed in Europe in the field of chemistry. I had the opportunity of working for a year in a European laboratory and was able to visit a number of university as well as industrial establishments. Most of the laboratories were conducting a vigorous program of fundamental research and on a larger

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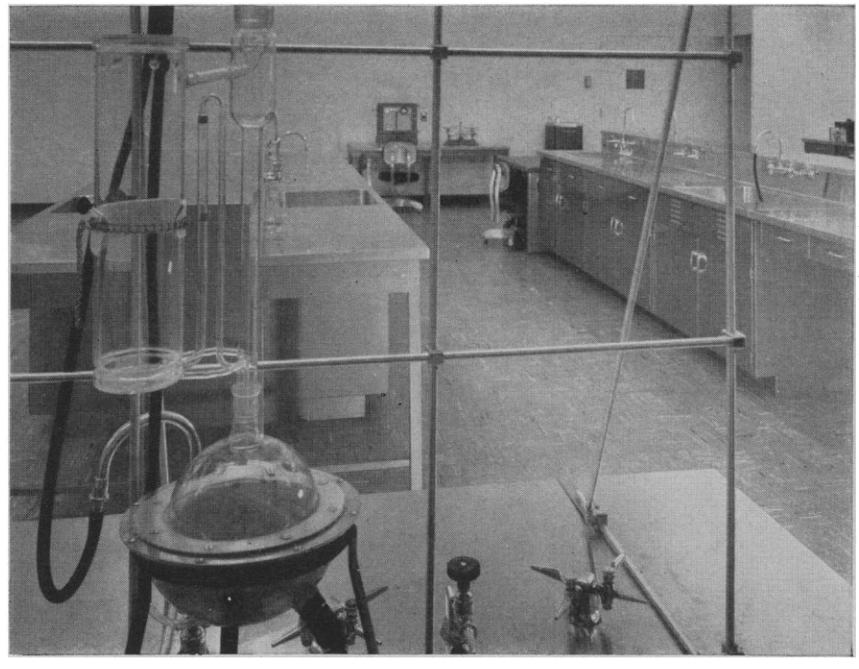

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