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The "Reaction Theory" of Respiratory Regulation

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(To be concluded).

The discovery of the reflex origin of the effect of O_2-lack makes inadmissible the original attempt of the Reaction Theory to attribute this effect to a centrogenic increase of C_H. So once more we stand before the question first formulated by PFLÜGER as to how the lack of a substance can act in an excitatory fashion. We can now pose the question whether our former explanation based on an accumulation of acid metabolic products during O_2-lack in the centres themselves cannot be applied to the aortic and carotic bodies. Can we not restate the Reaction Theory in such a way that the expression *glomerogenic* is substituted for the expression *centrogenic*?

A number of earlier experiments (see CORDIER and HEYMANS[2]) involving perfusion of the carotid sinus have demonstrated that the end-organs of the carotid nerve can be excited by an increase of C_H. SCHMIDT and coworkers[3] have shown that this is also true when all variations of CO_2-tension have been excluded. COMROE[4] has emphasized the fact that the sensitivity of the sinus nerves is sufficient to explain all cases of hyperpnœa during work attended by increase in blood-C_H.

That the same may well be the case in hyperpnœa due to O_2-lack has been indicated by a number of experiments from GESELL's laboratory:— WINDER[5] observed that anoxic excitation was either absent or eventually passed into a gradual depression when the isolated perfused sinus caroticus was poisoned with iodoacetic acid. From this she concluded that the anoxic stimulation of the chemoreceptors of the glomus caroticum depended on glycolytic processes, probably on a production of acid. Observations by WINDER and coworkers[6] that isolated ischæmia of the glomus leads to hyperpnœa, have similar indications. This is also true of the findings of BERNTHAL[7] concerning the behaviour of vascular reflexes originating from chemoreceptors. His researches showed that all factors producing an increase in C_H of the cell (anoxia, hypercapnia, cyanidæmia, excess of lactic acid) lead to an excitation of the vasoconstrictor centre, while factors producing a reduction of C_H resulted in vasodilatation. A rise of temperature which presumably leads to increase of C_H in the artificially perfused glomus is also followed by vasoconstriction and increase of respiratory movements; reduction of temperature has the opposite effect (BERNTHAL and WEEKS[1]).

However, much more convincing than these indirect conclusions are the experiments of EULER, LILJESTRAND, and ZOTTERMAN[2]. They measured the action potentials in the sinus nerves and showed that the impulses which are always present under normal conditions, became more frequent during oxygen lack as well as with increase of CO_2-tension and were abolished by increased pulmonary ventilation or oxygen supply. Reduction of the number of nerve fibres from which the impulses are led off, leads to a reduction in the frequency of the action potentials to an *equal* extent both for O_2-lack and stimulation by CO_2. This shows that the same nerve fibres are involved in the sensorial function, a fact to be expected from the Reaction Theory.

Still further, the action potentials produced by O_2-lack as well as by CO_2-stimulation vanish after injection of 0·5–2 ml of 0·5 *N* ammonia (the pressor effect remaining unaffected). In the same way action potentials caused by cyanide infusion can be eliminated by both O_2-supply and NH_3-injection. *All these experiments leave no other explanation possible except that it is the increase of C_H inside the glomus which causes nervous excitation both under conditions of increase of CO_2-pressure and under conditions of anoxæmia induced by a reduction of O_2-pressure. So even after the discovery of chemoreflex drives in regulation of respiration, the Reaction Theory retains its full validity, with the replacement of centrogenic by glomerogenic excitation.*

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[2] D. CORDIER and C. HEYMANS, *Le centre respiratoire* (Hermann & Cie, Paris 1935).

[3] C. F. SCHMIDT, J. H. COMROE jr., and R. D. DRIPPS, Proc. Soc. Exp. Biol. Med. *42*, 31 (1939).

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[2] U. v. EULER, G. LILJESTRAND, and Y. ZOTTERMAN, Skand. Arch. Physiol. *83*, 132 (1940).

Recently, GESELL[1] has attempted to replace the C_H-Theory of Respiratory Regulation by an *Acetylcholine Theory*, thus following the general fashion of referring all phenomena in the nervous system to acetylcholine. According to him, the effect of C_H depends on the anticholine-esterase activity of acids. In this way the level of concentration of acetylcholine produced and thereby the total magnitude and duration of excitation would be regulated. Indeed the prolongation of the effects of acetylcholine through an increase of C_H was proved in GESELL's laboratory in a number of investigations involving different organs.

But, a number of recent observations (see SÖZER and WINTERSTEIN[2]) make it appear doubtful whether acetylcholine is an "action substance" in the sense that it is the material responsible for conduction and transmission of excitation. Researches by HEYMANS and coworkers[3] have shown that different substances which completely abolish the activity of choline esterase leave breathing and respiratory reflexes unaffected. This result brings with it the conclusion that choline esterase plays no part, either direct or indirect, in the transmission of nerve impulses.

"Explanation" means reference of new phenomena to known principles. The action of C_H on the magnitude and speed of many chemical reactions, both in biology and in the chemistry of non-living systems, is a well-known phenomenon. The replacement of this widespread effect by a mechanism of which the general nature is unknown and whose existence is doubtful, appears to us at present to offer no advantage whatever.

When there is an adequate oxygen supply, the central respiratory control system continues to function even after permanent removal of the peripheral chemical regulatory mechanism (elimination of all chemoreceptors). This is true even when all *mechanical* regulation has ceased to function during artificial abolition of respiratory movements. WINTERSTEIN's experiment[4] proving the automatic nature of respiration—namely the continuation of action potentials in the phrenic nerve in curarized animals—is also successful after elimination of the chemoreceptors (WINTERSTEIN)[5]. Under these conditions too the magnitude of pulmonary ventilation is regulated by the C_H of the blood and vice versa. To what a precise degree this holds good even after elimination of the chemoreceptors was proved by the experiments of BANUS and coworkers[6]. In these experiments, after an intravenous injection of acid, increased ventilation —through a reduction of CO_2-tension—had restored the original p_H within 10–15 min. to within $\pm$ 0·01 p_H-units.

Similarly WINTERSTEIN[1] observed an *increase* of pulmonary ventilation and C_H of the blood, with simultaneous *reduction* of blood CO_2-tension, *during* injection of acid into animals whose chemoreceptors had been removed. This corresponds exactly to what happens in normal animals and shows once more that it is C_H and not carbonic acid which regulates the extent of breathing. WINTERSTEIN's observation on the effect of O_2-lack on animals without chemoreceptors take the form of a veritable *experimentum crucis* against the carbonic acid theory. In such animals, as we have seen, there is no sign of increase of respiratory movements, on the contrary, there is a *decrease of pulmonary ventilation* which leads to an *increase of* CO_2*-tension*. Thus in the first case there is a *reduction of* CO_2*-tension* and an *increase in respiratory movements*, and in the second case a *reduction of breathing* during *increase of* CO_2*-tension*. There could hardly be a clearer and more convincing demonstration of the *lack of dependance of pulmonary ventilation on carbonic acid*.

After removal of the chemoreceptors, the C_H of the blood usually decreases during oxygen-deficiency respiration, clearly as a result of the greater extent of reduction of oxyhæmoglobin. However, this is probably not sufficient to explain the reduction of pulmonary ventilation. It seems probable that, when the hypoxic reinforcement of respiratory movements by the chemoreceptors is no longer present, the amount of energy of oxidation at the disposal of the centres is no longer adequate to maintain their normal activity. Before the discovery of the effect of the chemoreceptors, GESELL and coworkers[2] had performed experiments in which the pulmonary ventilation was kept constant by artificial respiration with opened thorax. Under these circumstances oxygen-deficiency respiration leads to a reduction of oxygen consumption, and hence energy production calculated from it.

The chemoreflexes are characterized by their extraordinary powers of resistance. For these reasons it is possible to explain the observations mentioned above (see p. 224, 2nd col.), of a number of authors (COMROE and SCHMIDT[3], BENZINGER and coworkers[4], BEECHER and MOYER[5]), namely, that the respiratory centres lose their capacity to be influenced by carbonic acid during very deep anæsthesia, especially with certain specific anæsthetics. Under these conditions only the receptor reflexes produced by O_2-lack are maintained and may

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[3] J. H. COMROE jr. and C. F. SCHMIDT, Amer. J. Physiol. *121*, 75 (1938).

[4] TH. BENZINGER, E. OPITZ, and W. SCHOEDEL, Pflügers Arch. 241, 71 (1938/39).

[5] H. K. BEECHER and C. A. MOYER, J. Clin. Invest. *20*, 549 (1941); C. A. MOYER, J. Thorac. Surgery *11*, 131 (1941); C. A. MOYER and H. K. BEECHER, J. Clin. Invest. *21*, 429 (1942).

even be accentuated. Their functional elimination by means of high O_2-pressures can bring respiratory movements to a complete standstill. So COMROE and SCHMIDT have designated the chemoreflexes as the *ultimum moriens* of the respiratory mechanism.

Recently, a number of fundamental investigations have appeared concerning *the part played in regulation of respiration by the directly central factors (hæmatogenically controlled) and by factors due to reflexes originating in the chemoreceptors (glomerogenically controlled factors)*.

GOLLWITZER-MEIER and LERCHE[1] performed experiments in which continuous p_H-measurements were made in the isolated carotid-sinus circulation as well as in the arterial blood of the general systemic circulation. They found that the respiratory centres possess a lower threshold than the chemoreceptors of the glomus caroticum during respiration of gas mixtures rich in CO_2, that is to say during *hæmatogenic* increase of C_H. On the other hand all investigations show complete agreement that the effect of O_2-tension is *glomerogenic*. GESELL and coworkers[2] as well as BJURSTEDT[3] have estimated the part played by chemoreceptors by means of reversible cold-block of the carotid nerves after section of the vagi. GERNANDT[4] discovered that the chemoreceptors could be selectively put out of action by local injection of 0·5 *N* acetic acid. This method made it also possible to estimate the part played by the different chemoreceptors, and to confirm the fact demonstrated by earlier experiments that the influence of the chemoreceptors of the glomus aorticum was very inferior to that of the chemoreceptors of the glomera carotica.

The reduction of breathing after elimination of the chemoreceptors shows that they are continually active under normal conditions. This fact already discovered by EULER and coworkers[5] in previously mentioned experiments, was confirmed by GESELL and coworkers and especially by the researches of GERNANDT.

In apparent contradiction we have the repeated observation of increase of respiratory movements in human beings breathing pure oxygen. This has been established by HECK[6], WATT and coworkers[7] and by ALVERYD and BRODY[8]. BINET and STRUMZA[9] were only able to observe a depressing effect of breathing oxygen in chloralized dogs, but not in the normal animal. One must bear in mind that breathing oxygen produces two opposed effects:— the elimination of the normal chemoreflex drive must have a reducing effect on pulmonary ventilation, whereas the decrease in reduction of oxyhæmoglobin must increase the difficulty of removal of carbonic acid and must therefore also increase the C_H of the tissues and so lead to a reinforcement of pulmonary ventilation. The end result will therefore depend on which of these factors predominates.

The reduction of respiratory movements on elimination of the chemoreceptors shows that the normal O_2-tension of the blood is sufficient for their excitation, an excitation which will become stronger and stronger the more the O_2-tension of the blood (and therefore in the glomus) falls. However, according to GESELL's school, this effect of stimulation of the chemoreceptors is also dependant on the prevailing CO_2-tension. The greater this CO_2-tension is, the smaller the influence of the chemoreceptors; the smaller it is, the greater their effect. Thus the apnœa caused by CO_2-lack due to hyperventilation is considerably prolonged by elimination of the chemoreceptors, and may even lead to death of the animal, as HEYMANS and JACOB[1] have shown.

With CO_2-pressures above 5–6% the chemoreceptors according to GESELL are completely ineffective, and regulation of respiration is purely central. However, as we have seen above, this is not the case during certain kinds of deep anæsthesia, where the respiratory centres have completely lost their sensitivity to CO_2, and respiration is only maintained by the more resistant chemoreceptors.

As accepted by GESELL too, the hyperpnœa of O_2-lack is purely glomerogenic, so that sudden cold-block of the carotid nerves produces an apnœa which may easily lead to the death of the animal.

BJURSTEDT[2] registered simultaneously the pulmonary ventilation, the oxygen saturation and the C_H of the blood of dogs, and investigated the effect of elimination of chemoreceptors by cold-block during acute O_2-lack and during O_2-lack lasting many hours.

The results of the experiments with acute O_2-lack agreed in essentials with those of GESELL and coworkers. After section of the vagi cold-block of the carotid nerves during hypoxic hyperpnœa produces a reduction of respiratory movements which goes entirely parallel to the increasing alkalinity of the blood, thus proving that the *central*[3] impulses are reduced ac-

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[9] L. BINET and M. V. STRUMZA, C. R. Soc. Biol. *141*, 3 (1947).

[1] C. HEYMANS and J. JACOB, Arch. int. Pharmacod. *75*, 111 (1947).

[2] A. G. H. BJURSTEDT, Acta physiol. Scand. *12*, Suppl. *38*, 1 (1946).

[3] Both BJURSTEDT and GESELL speak of *centrogenic* impulses. This expression seems to me inept and liable to lead to misunderstandings. I have introduced the expressions centrogenic and hæmatogenic *hyperpnœa* to characterize states in which the observed hyperpnœa was *primarily* due to changes in the metabolism of the centres or due to changes in the composition of the blood. *Respiratory drives* are always centrogenic, since they originate in the respiratory centres themselves. They may, however, be induced either directly *centrally* or by *way of reflexes* (glomerogenic).

cording to the lowering of the C_H. That this reduction is due to the change in C_H and not to a paralysis of the respiratory centres through O_2-lack is indicated by the following considerations:– the reduction of respiratory movements, which sometimes can lead to complete cessation of breathing, naturally produces a new rise in C_H; this leads to a new increase of respiratory movements; on the contrary if there were an anoxic paralysis of the centres this paralysis could only be increased by a reduction of pulmonary ventilation. Further as we shall presently see in discussing experiments on chronic oxygen lack, the reduction of C_H and suppression of respiratory movements becomes less the longer the duration of hypoxia, while a paralysing effect of O_2-lack should become more pronounced the longer it lasts. Hypoxic hyperpnœa, however, is itself entirely dependant on the chemoreceptors, and it can happen—as in GESELL's experiments mentioned above —that respiration is maintained entirely by the chemoreceptors (that is by glomerogenic drive) when the C_H of the blood is very low. Under these conditions elimination of chemoreceptor drive by cold-block can bring breathing to a standstill.

In hypoxia of long duration (9–10 hours) the alkalinity due to the hyperpnœa gradually disappears entirely, clearly by compensatory migration of alkaline materials from the blood. At the same time the glomerogenic chemoreflex drive becomes continually less, the central drive comes more and more into the foreground until at length it controls breathing almost completely. Then cold-block of the carotid nerve remains without effect. In one case it was possible to reverse the experiment so that, after hypoxia of five hours duration, followed by two hours respiring 100% O_2, the chemoreceptor block again became effective.

As a result of his experiments, BJURSTEDT comes to the conclusion that the activity of the centres is regulated by the C_H of the blood with which it goes completely parallel. So far it entirely supports the correctness of "WINTERSTEIN's first Reaction Theory" —namely of the regulation of breathing by the C_H of the blood. On the other hand, the effect of O_2-lack, depending as it does on chemoreceptors (i. e. the glomerogenic chemoreflex drive), in an exactly opposite fashion would be greater the more alkaline the blood is.

However, this conclusion of BJURSTEDT, based on the apparent parallelism between the glomerogenic chemoreflex drive and the alkalinity of the blood, stands in direct contradiction to experiments we have mentioned above (see p. 261). In these experiments— particularly of SCHMIDT and coworkers[1]—the excitatory effect of *increased* C_H was established for the artificially perfused sinus. BJURSTEDT's conclusion is also contradicted by certain observations which he himself has not contested:– ZOTTERMAN[1] demonstrated increase in the action potentials in the carotid nerves during CO_2-inspiration and intravenous injection of acid. Further EULER and coworkers[2], in experiments mentioned above (see p. 261), showed that action potentials caused by excess of CO_2 or O_2-lack could be abolished by NH_3-injections. It therefore seems clear that the experimental results have been misinterpreted by BJURSTEDT.

His own data show the way to a solution of this contradiction. He himself points out that the increase of glomerogenic drive with increasing alkalinity of the blood might be due to O_2-lack, since the O_2-*tension* of the blood falls with decrease of C_H, although the O_2-*saturation* may remain the same. He believes, however, that this explanation could not satisfy all cases, since sometimes hyperventilation continues to increase in spite of the increase in O_2-saturation to which it leads. As a direct proof of the dependance of the intensity of the glomerogenic drive on C_H in a sense *contrary* to that indicated by the Reaction Theory, BJURSTEDT quotes the following experiments:– in the course of respiration with reduced O_2-supply, he further lowered the latter by rebreathing, but in spite of the *increase of* C_H caused by this procedure, he noted a *reduction of hyperpnœa*. BJURSTEDT has clearly underestimated the extent of the effect of C_H on O_2-tension. We have attempted to calculate the changes in O_2-tension in this case which he considered to be so especially convincing. As a result we have found that, in spite of the *reduction of the* O_2-*saturation* of the blood, the increase in C_H has occasioned an *increase in* O_2-*tension*, which might well be sufficient to explain the decrease in glomerogenic drive and the consequent decrease of hyperpnœa.

The calculation was made on the basis of HILL's formula

$$\frac{y}{100} = \frac{K x^n}{1 + K x^n}$$

where x is the O_2-tension, y the O_2-saturation and n and K constants, and on the basis of the PETERS-BARCROFT graph, of which the coordinates are p_H and –log K. Here the unproved but (since we are dealing with comparative estimations) justifiable assumption has been made that the constants are the same for canine and human blood (see HASSELBALCH[3]). On this basis the O_2-tension *before* re-breathing was 23·2 mm Hg and *after* re-breathing 26·5 mm Hg.

If we summarize the results of all the investigations we have discussed, we get the following *picture of the chemical regulation of respiration.*

That activity of the respiratory centres which is of *central origin* goes entirely parallel with the reaction of the blood and, as far as *hæmatogenic regulation* of breathing is concerned agrees completely with the

[1] C. F. SCHMIDT, J. H. COMROE jr., and R. D. DRIPPS, Proc. Soc. Exp. Biol. Med. *42*, 31 (1939).

[1] Y. ZOTTERMAN, Skand. Arch. Physiol. *72*, 73 (1935).

[2] U. v. EULER, G. LILJESTRAND, and Y. ZOTTERMAN, Skand. Arch. Physiol. *83*, 132 (1940).

[3] K. A. HASSELBALCH, Biochem. Z. *78*, 134 (1916).

Reaction Theory. The effect of *lack of oxygen* is entirely reflex by way of the chemoreceptors, whose activity—again in complete agreement with the *Reaction Theory*—depends on the *intracellular hydrogen-ion concentration in the glomus*. This *glomerogenic regulation* of respiratory movements in hypoxia leads to increase of alkalinity of the blood on account of the induced hyperpnœa. This increase in alkalinity for its part reduces the oxygen tension of the blood for the same oxygen saturation, thus increasing again the intracellular C_H in the glomus and consequently reinforcing hyperpnœa by chemoreflex drive. Thus the apparent disadvantage of increase in alkalinity of the blood during hyperpnœa by oxygen lack proves in the end to be advantageous.

If one seeks for a teleological explanation of this peculiar mechanism of glomerogenic regulation of breathing, we may assume with GESELL[1] that a peripheral mechanism came into existence to protect the vitally important centres with their great oxygen demands—a mechanism which reacts with the greatest sensitivity to any reduction of oxygen tension. No special mechanism is necessary for the easily diffusible and relatively innocuous carbonic acid. Here, the great sensitivity of the respiratory centres to any change in C_H is sufficient to initiate any necessary changes in respiratory movements.

Zusammenfassung

Es ist seit langem bekannt, daß sowohl O_2-Mangel wie CO_2-Anhäufung eine Verstärkung der Atmung herbeiführen. Um die Wirkung dieser beiden Faktoren auf einheitlicher Grundlage zu erklären, wurde der Gedanke geäußert, daß O_2-Mangel die Erregbarkeit der Atmungszentren für CO_2 erhöhe oder umgekehrt. Aber Änderung der Erregbarkeit ist nichts anderes als eine Umschreibung der Beobachtung, daß die Wirkung eines Reizes unter bestimmten Bedingungen größer oder kleiner ist als unter anderen. Über die Ursache dieses Verhaltens wird nichts ausgesagt. Ein wirklicher Versuch, die Wirkungen dieser beiden Faktoren einheitlich zu erfassen, wurde durch die *Reaktionstheorie der Atmungsregulation* unternommen. Nach dieser Theorie beruht die erregende Wirkung der Kohlensäure auf ihrer Natur als *Säure* und jene des O_2-Mangels auf der Anhäufung *saurer* Stoffwechselprodukte in den Atmungszentren. Dies bedeutet, daß in beiden Fällen der wirksame Faktor von einer *Steigerung der* C_H dargestellt wird. Im ersteren Falle würde es sich um eine *hämatogene*, im zweiten um eine *zentrogene* Steigerung handeln.

Eine große Zahl von Beobachtungen sprechen zugunsten dieser Theorie, am überzeugendsten jene, in denen CO_2-Spannung und C_H sich in entgegengesetzter Richtung ändern und die Änderung der Lungendurchlüftung der letzteren parallel geht, wie dies bei Säureinjektion der Fall ist. Die scheinbar abweichende Wirkung von Bikarbonatinjektionen findet ihre Erklärung in der rascheren Diffusion der undissoziierten Kohlensäure. Die mangelhafte quantitative Übereinstimmung zwischen der Wirkung von $CaCl_2$- oder NH_4Cl-Azidosen einerseits und CO_2-Inhalationen andererseits läßt sich auf die Wirkung des eingebrachten Kations zurückführen.

Eine neue Periode der Lehre von der chemischen Atmungsregulation begann mit der Entdeckung der *Chemorezeptoren* (Karotis- und Aortennerven), besonders mit dem Nachweis, daß der Ursprung der *hypoxischen Hyperpnöe* nicht zentral ist, sondern im *Glomus aorticum* und vor allem in den *Glomera carotica* gelegen ist. Es war daher eine Modifikation der Reaktionstheorie erforderlich, in dem Sinne, daß die Steigerung der C_H, durch welche die hypoxische Hyperpnöe bedingt wird, nicht zentrogen, sondern *glomerogen* ist. Zahlreiche Beobachtungen sprechen für diese Auffassung. Der entscheidende Beweis ihrer Richtigkeit wurde durch die Feststellung geführt, daß die bei O_2-Mangel und die bei CO_2-Anhäufung erzeugten Impulse durch die gleichen Nervenfasern geleitet und beide durch NH_3-Injektion, also durch Herabsetzung der C_H, beseitigt werden. So bleibt also die Reaktionstheorie auch nach Entdeckung der Chemorezeptoren von Bestand, nur muß der Ausdruck *zentrogen* durch *glomerogen* ersetzt werden.

Nach Ausschaltung der Chemorezeptoren bleibt die automatische Tätigkeit der Atmungszentren unter gewöhnlichen Bedingungen erhalten und wird wie beim normalen Tier durch die C_H des Blutes reguliert. Hingegen bewirkt O_2-Mangel keine Hyperpnöe mehr; er kann sogar eine Hypopnöe herbeiführen, die zu einer Steigerung der CO_2-Spannung Anlaß gibt. Dies ist ein *experimentum crucis* gegen die CO_2-Regulationstheorie: Säureinjektion (mit oder ohne Ausschaltung der Chemorezeptoren) erzeugt eine Herabsetzung der CO_2-Spannung mit Atmungssteigerung; O_2-Mangel nach Chemorezeptorenausschaltung bewirkt eine Steigerung der CO_2-Spannung mit Atmungsverminderung.

Untersuchungen über den Anteil der direkt zentralen und der chemoreflektorischen Impulse an der Regulierung der Atmung ergeben, daß die ersteren gegen Kohlensäure eine niedrigere Reizschwelle zeigen als die letzteren und daß ihre Größe der C_H des Blutes völlig parallel geht. Sinkt diese unter ein gewisses Niveau, so wird die Atmung nur durch die Chemorezeptoren erhalten und erlischt bei deren Ausschaltung. – Die Wirkung des O_2-Mangels wird ausschließlich durch die Chemorezeptoren vermittelt, deren Tätigkeit von der intrazellularen C_H im Glomus abhängt. Die glomerogene Atmungsverstärkung bewirkt eine Alkalisierung des Blutes, die dessen O_2-Spannung herabsetzt. Diese Herabsetzung erzeugt wieder eine Steigerung der C_H im Glomus und dadurch eine weitere Verstärkung der Atmung. So steht die hypoxische Verminderung der Blut-C_H, die scheinbar der erforderlichen Atmungsverstärkung entgegenwirkt, in Wirklichkeit auch im Dienst der Atmungsregulation.

[1] R. GESELL, Ergebn. Physiol. *43*, 477 (1940).