EXPERIENTIA

Vol. V - Fasc. 6 Pag. 221–260 15. VI. 1949

The "Reaction Theory" of Respiratory Regulation

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Our knowledge of the chemical regulation of respiration which seemed at least to a certain degree to be a finished chapter, has lately undergone such surprising modifications that it appears desirable to present a comprehensive review of the subject on a historical basis. In earlier days it was customary to distinguish between a nervous and a chemical regulation. But recent discoveries have shown that this division is no longer useful since a great part of chemical regulatory processes take place through nervous channels. It is therefore better to differentiate between mechanisms regulating breathing, on the basis of the factors which are responsible for them, rather than on the channels through which they are operative. We shall therefore distinguish between *mechanical factors* (respiratory movements) and *chemical factors* (composition of the blood, metabolism of the responsible nervous mechanisms) concerned with regulation. In this review, only the second category will be considered.

The basis of our knowledge of chemical regulation of the respiratory act was laid down by PFLÜGER[2] who showed 80 years ago that both an increase of the carbon dioxide content and a decrease of the oxygen content, even if acting separately, produced an increase in pulmonary ventilation. The researches of J. S. HALDANE and his coworkers showed that, under normal conditions, the CO_2-content of the blood can be considered to be the chemical regulator of breathing. This was the state of our knowledge at the beginning of the century, as summarized by DOUGLAS[3], HALDANE'S chief colleague.

The unmistakable similarity of the effects of O_2-lack and CO_2-excess in spite of certain differences of detail, from the earliest days lead to attempts to reduce the two factors to a common basis. But such attempts were essentially confined to consider one of the factors as the "true" or "only operative" factor, and the other as playing the part of a *sensitizer* of the respiratory centre with respect to the first factor. Sometimes O_2-lack and sometimes CO_2-excess was considered to be the "true respiratory stimulus", excitability to which was increased by CO_2-excess or O_2-lack, or vice versa. Such attempts have been continued until very recent times, as we shall see later. But the problem thus postulated is imaginary. As WINTERSTEIN[1] has striven to emphasize, "excitability" in the *absolute* sense is a meaningless conception, and can only take on meaning through comparison, namely its values are *relative*. Excitability in biology means nothing more than the ability of a living system to respond to a particular stimulus by a reaction of particular magnitude. If the same stimulus produces a reaction of less magnitude than before, we say that the excitability is reduced, and, if the reverse happens, is increased. The word "excitability" is therefore nothing more than a short, expedient word, expressing with economy of thought a change in magnitude of reaction with respect to the same stimulus, or the attainment of the same magnitude of reaction with respect to a stimulus of different magnitude. That this expression can serve in an "explanatory" sense, that is to say by enabling subsequent reproduction of the events in thought processes, is impossible.

Let us suppose that, following the customary scheme, I say "O_2-lack increases the sensitivity of the respiratory centre with respect to CO_2", this is nothing more or less than a shorthand expression of the observation that during O_2-lack, the same CO_2-concentration as before produces a greater effect, or that the same effect can be produced by a lower concentration than under usual conditions. But nothing has been "explained", nothing has been said at all about the cause of the event. It is equally clear that we have complete liberty to consider either of the factors as the independant variable, with the other as the dependant variable. In just the same way that we can say that availability of oxygen alters the excitability of the respiratory centre with respect to carbonic acid, so we can equally well state that carbonic acid concentration determines the excitability of the respiratory centre with respect to oxygen. But from the point of view of economy of thought, it is simpler to choose as the independant variable that factor which undergoes the most frequent changes. HALDANE was thus completely

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[2] E. PFLÜGER, Pflügers Arch. *1*, 61 (1868).

[3] C. G. DOUGLAS, Ergebn. Physiol. *14*, 338 (1914).

[1] H. WINTERSTEIN, *Kausalität und Vitalismus* (2. Aufl., Springer, Berlin 1928).

justified when he considered the CO_2-tension in the blood to be the normal respiratory regulator, because it was precisely this factor which underwent the most frequent changes, as far as the knowledge at that time extended.

If one intends to attempt to refer all factors which influence some particular phenomenon back to a single factor, this cannot be done by a manipulation of excitability, but by proving that all the different modifying factors can themselves be referred back to one and the same factor which is common to them all. Such an attempt has been made in WINTERSTEIN's "Reaction Theory" with respect to respiratory regulation by O_2 and CO_2.

Studies on the effects of CO_2 on the central nervous system had led WINTERSTEIN[1] to the conclusion that two factors could be distinguished, a primary depressing factor corresponding to the specific narcotic properties of carbonic acid, and a secondary excitatory one. The correctness of this conclusion has been lately confirmed by DRIPPS and COMROE[2] in experiments on man where air containing high CO_2-concentrations was inhaled.

In 1910 WINTERSTEIN[3], in experiments on new-born animals, proved that the respiratory excitatory effect of carbonic acid could also be produced by other acids, a fact which led him to the conclusion that the secondary excitatory effect of carbonic acid is due to its nature *as an acid*. As it was known that acid is produced in organs suffering from O_2-lack, it seemed possible to refer both O_2-lack and CO_2-excess to a single common factor, namely the *hydrogen-ion concentration* (C_H) of the blood.

This "Theory of Respiratory Regulation by the C_H of the Blood" of course did not mean that there is some action at a distance of the blood on the cells of the respiratory centre, it was simply based on the supposition that the C_H of these cells will change in the same direction as that of the blood. However, a few years later WINTERSTEIN[4] discovered the fact that under conditions of O_2-lack the reaction of the blood is not pushed towards the acid side, on the contrary it becomes more *alkaline*. He explained this phenomenon quite simply as follows:—"the dyspnœa of oxygen lack is the result of metabolic changes, namely the accumulation of products of asphyxiation *in the respiratory centre itself*, without being preceded by any change in the composition of the blood"[5]. The increased respiratory movements lead to increased washing out of CO_2 and so to greater alkalinity of the blood. Thus, in O_2-lack, it is not the reaction of the blood which causes a change in pulmonary ventilation, on the contrary, it is the change in pulmonary ventilation which causes a change in the reaction of the blood. The reason for this appeared to be quite simple, namely that the central nervous system is, as is well known, the organ which suffers first of all from oxygen lack. PFLÜGER had already noticed the acidification of the cerebral cortex which appears quickly after death, and WINTERSTEIN[1] observed a reversible acidity in the living spinal cord of the frog, under conditions of O_2-lack.

In consequence of this, WINTERSTEIN[2] restated his "Reaction Theory" in more precise terms in 1921, and distinguished between *hæmatogenic hyperpnœa* due to preceding accumulation of acid in the blood (carbonic acid, lactic acid, acids of pathological origin, causing rise of C_H or *hyperhydria*), and *centrogenic hyperpnœa* as a result of the metabolism of the centres themselves. A few years later, GESELL[3] put forward a theory of chemical respiratory regulation in principle identical with the above.

If the reaction of the blood regulates the degree of pulmonary ventilation and so the CO_2-output, so, as PORGES and his coworkers[4] first expounded, breathing must be a regulator of the reaction of the blood. HASSELBALCH[5] confirmed how completely this is true, by showing that, under nutritional conditions in which the base-acid supply was varied within extreme limits (with corresponding extreme variations in the reaction of the urine), the reaction of the blood remained practically constant on account of regulation of CO_2-exhalation.

This newly discovered function of *breathing as a regulator of blood reaction* referred, however, only to hæmatogenically controlled changes of respiration, while the centrogenic (or, as we shall see later, glomerogenic) hyperpnœa has the contrary effect of upsetting the reaction by increasing the alkalinity of the blood.

The details of the dispute about the question whether the respiratory excitatory effect of carbon dioxide depends on its specific nature or on its nature as an acid, cannot be followed here. The reader is referred to the summarizing reports of WINTERSTEIN[6], GESELL[7], HESS[8], and especially of NIELSEN[9]. Only two points of

[1] H. WINTERSTEIN, Arch. Anat. Physiol., Physiol. Abt. (1900), Suppl., S. 177.

[2] R. D. DRIPPS and J.H. COMROE, jr., Amer. J. Physiol. *149*, 43 (1947).

[3] H. WINTERSTEIN, VIII. Int. Physiol. Congreß Wien, 1910. – Pflügers Arch. *138*, 167 (1911).

[4] H. WINTERSTEIN, Bioch. Z. *70*, 45 (1915).

[5] ..."daß die Sauerstoffmangel-Dyspnöe durch die Stoffwechselvorgänge, nämlich durch die Ansammlung von Erstickungsstoffen *in den Atemzentren selbst* ausgelöst wird, ohne daß eine Änderung in der Blutbeschaffenheit vorausginge".

[1] H. WINTERSTEIN, Bioch. Z. *70*, 130 (1915).

[2] H. WINTERSTEIN, Pflügers Arch. *187*, 293 (1921).

[3] R. GESELL, Amer. J. Physiol. *66*, 5 (1923).

[4] O. PORGES, A. LEIMDÖRFER, and E. MARCOVICI, Wiener klin. Wschr. Nr. 40 (1910); Z. klin. Med. *73*, 389 (1911).

[5] K. A. HASSELBALCH, Bioch. Z. *46*, 403 (1912).

[6] H. WINTERSTEIN, Naturwissenschaften *11*, 625, 645 (1923). – Klin. Wschr. *7*, 241 (1928).

[7] R. GESELL, Physiol. Reviews *5*, 551 (1925); Ergebn. Physiol. *28*, 340 (1929).

[8] R. W. HESS, *Die Regulierung der Atmung* (Thieme, Leipzig 1931).

[9] M. NIELSEN, Skand. Arch. Physiol. *74*, Suppl. *10*, 83 (1936).

particular importance must be emphasized. First, under ordinary conditions both CO_2-tension and C_H of the blood change in the same direction, so that it is impossible to distinguish which is the factor responsible for the effects produced. The most conclusive arguments either for or against the Reaction Theory must, therefore, come from experiments in which the two factors change in opposed directions. This was indeed the case in the above-mentioned experiments of HASSELBALCH involving an acid diet, and an even more marked condition was obtained by *injection of acid* into the circulatory system (WINTERSTEIN[1], WINTERSTEIN and FRÜHLING[2]). In both series of experiments the magnitude of pulmonary ventilation varied according to the C_H and against the CO_2-tension. An apparently contradictory behaviour results from the *injection of bicarbonate*, after which the hæmatogenic changes in respiratory movements occur contrary to the changes of C_H of the blood (increased pulmonary ventilation with more alkaline blood reaction). This behaviour seems to have been completely cleared up by an observation first made by JACOBS[3], namely that an *alkaline* $H_2CO_3/NaHCO_3$-solution gives an acid taste on account of the more rapid diffusion of undissociated carbonic acid, and similarly pushes the reaction of animal and plant-cells over towards the acid side. This same behaviour was reproduced in a non-living model (WINTERSTEIN[4]). Finally GESELL and HERTZMAN[5] brought direct proof that injection of $NaHCO_3$ into the blood produced on the one hand a shift of the reaction of the blood towards the alkaline side, but on the other hand a shift of the reaction of the cerebro-spinal fluid and doubtless therefore of the cells of the central nervous system too, towards the acid side. Thus these experimental facts are completely in accord with the changes in pulmonary ventilation to be expected from the Reaction Theory.

The second point is the question of the *quantitative* agreement between the respiratory effects of carbonic acid on the one hand and other acids on the other hand, which would be postulated by the Reaction Theory. One of the most weighty arguments in favour of a specific effect of carbonic acid is an observation made by numerous authors that, with CO_2, a large increase in magnitude of breathing occurs with a relatively much smaller change in C_H of the blood.

Here it must be stated *a priori* that in the majority of experiments a direct quantitative agreement cannot be expected for three reasons. Firstly it cannot be expected on account of the peripheral excitatory effect of carbonic acid (see WINTERSTEIN[1]). This explains why *inhaling* air rich in CO_2 produces a relatively greater increase of breathing. If the carbonic acid is directly injected into the blood, the difference between the effects of this and other acids disappears more or less completely (WINTERSTEIN[2]).

Secondly, foreign acids introduced into the organism often bring along with them other *kations*, which themselves may have an influence on the magnitude of pulmonary ventilation. Indeed, we shall consider some of these cases in a moment. Thirdly, as we have already seen in the experiments mentioned above, the cell permeability with respect to undissociated carbonic acid is much greater than with respect to ions, so that, in experiments of short duration, the intracellular C_H-changes produced are greater and more speedily realized with carbonic acid than with other acids.

The opponents of the Reaction Theory will therefore draw their strongest arguments not from C_H-changes of short duration but from changes lasting over considerable periods, such as those which have lately been produced by NIELSEN[3] in his comprehensive series of researches. NIELSEN first of all calls attention to the work of HALDANE and his coworkers[4] who produced in themselves considerable degrees of hyperhydria by taking large doses of ammonium chloride. In these experiments the p_H of the blood fell from 7·41 to 7·29. According to NIELSEN the Reaction Theory demanded as a consequence a huge increase in pulmonary ventilation, whereas in reality the reduction of the alveolar CO_2-tension showed that it increased only twofold. This same criticism was put forward by NIELSEN not only on the basis of numerous older experiments with NH_4Cl- and $CaCl_2$-acidosis, but chiefly as the result of his own observations.

NIELSEN compared the increase of breathing during NH_4Cl-acidosis persisting for several days, with that produced by inhalation of air rich in CO_2 for a period of hours. On one subject he found an increase of pulmonary ventilation of 10 l p. min. in the case of CO_2, but of only 0·3–0·7 l p. min. in the case of NH_4Cl, although the change in p_H of the blood was only 0·04 to 0·045 in the case of CO_2 compared with 0·6–0·8 in the case of NH_4Cl. Since in this experiments of considerable duration there could be neither any question of reflex stimulatory action of carbonic acid, nor in the NH_4Cl-experiments any question of incomplete C_H-equilibrium between blood and tissue cells, according to NIELSEN's view they represent a decisive proof that the Reaction Theory is incorrect.

[1] H. WINTERSTEIN, Bioch. Z. *70*, 130 (1915).
[2] H. WINTERSTEIN and G. FRÜHLING, Pflügers Arch. *234*, 187 (1934).
[3] M. H. JACOBS, Amer. J. Physiol. *51*, 321; *53*, 457 (1920); J. General Physiol. *5*, 181 (1922).
[4] H. WINTERSTEIN, Naturwissenschaften *11*, 625 (1923).
[5] R. GESELL and A. B. HERTZMAN, Amer. J. Physiol. *78*, 610 (1926).

[1] H. WINTERSTEIN, Arch. Anat. Physiol., Physiol. Abt. (1900), Suppl. S. 177.
[2] H. WINTERSTEIN, Bioch. Z. *70*, 130 (1915). – Pflügers Arch. *222*, 411 (1929).
[3] M. NIELSEN, Skand. Arch. Physiol. *74*, Suppl. *10*, 83 (1936).
[4] J. B. S. HALDANE, G. C. LINDES, R. HILTON, and F. R. FRASER, J. Physiol. *65*, 412 (1928).

We have already mentioned above that the introduction of new ions or the unbalanced increase of concentration of one particular kind of ion can cause unpredictable complications. Disturbances of the ionic equilibrium can produce changes of respiratory activity in spite of constant C_H, as in particular the researches of GOLLWITZER-MEIER[1] have shown. As HALDANE[2] had observed, increase in the concentration of the NH_4-ion leads to an increase in the calcium level, the effect of which in depressing pulmonary ventilation has been demonstrated (see VERSTAETEN[3]). But, leaving this out of account, it is difficult to see how the acidosis experiments can provide an argument for the specific effect of carbonic acid. For, even if the increase of breathing does not agree *quantitatively* with the predictions of the Reaction Theory, according to the CO_2-regulation Theory there should have been no increase, on the contrary, there should have been a marked *decrease* of pulmonary ventilation. As an exemple we may quote the experiment of HALDANE where the alveolar CO_2-tension, and therefore that of the blood fell from 35 to as low a value as 18 mm Hg.

NIELSEN explains all these contradictions, especially the behaviour during O_2-lack, by the magic wand of "changes in excitability". These were measured by LINDHARD'S method, where the extent by which the actual CO_2-tension exceeds the CO_2-tension at "the point of apnœa" is determined. The steepness of the curve which is obtained when these differences are plotted as abscissæ and the pulmonary ventilation as ordinates, gives a measure of the "excitability of the respiratory centre". This was shown to be higher both under conditions of O_2-lack and during NH_4-acidosis. As we explained at the beginning, the demonstration of an "increase of excitability" is nothing more than a redescription of the observation that any stimulus—here the CO_2-tension or its increase—can, under certain circumstances, produce a greater effect than usual, without, however, any explanation being involved. Let us assume, in accordance with the Reaction Theory that the magnitude of pulmonary ventilation depends on the C_H of the centres, the C_H itself depending centrogenically on H-ions produced during metabolism, and hæmatogenically on H-ions brought to the centres by the blood. It now becomes obvious that any increase of the prevailing C_H, whether caused by increased intracellular acidity during O_2-lack or by acidification of the blood during acidosis, will decrease the magnitude of the additional stimulus needed to produce any determined effect. Thus NIELSEN'S observation that the "excitability curve" with respect to C_H shows the same form as it does with respect to CO_2-tension, is in no way opposed to the Reaction Theory as the author believes, but, on the contrary, stands in complete agreement with it. In addition, BJURSTEDT[1] has rightly drawn attention to the fact that the reduction of the alkali reserve during acidosis must, with the same change of CO_2-pressure, lead to a greater C_H-change, that is to say to an "increase in excitability".

NIELSON has devoted the greater part of his investigations to proving that hyperpnœa during work cannot be explained by a simple change in C_H. But since all available research shows that this hyperpnœa is an extremely complex phenomenon seeming to involve central and reflex impulses, circulatory and hæmatogenic changes, whose interrelations are still incompletely understood, no conclusions either for or against the Reaction Theory can be drawn from it. It is impossible, however, to deal with the extensive literature on the subject here.

Jugglery with the conception of excitability to "explain" respiratory regulation has been perpetuated in numerous more recent works (reviewed in OPITZ[2]). Thus BENZINGER and his coworkers[3] in all earnest pose the question—the question which we mentioned in the introduction as the paradigm of the imaginary problem—whether O_2-lack increases the CO_2-excitability, or whether carbonic acid increases excitability to lack of oxygen. However, the observation which led the authors to put forward their question, is worth mentioning. They found that dogs under deep morphine-pernocton anæsthesia to a large extent lost their sensitivity to CO_2, so that an admixture of even 12% CO_2 with the inspired air remained ineffective. The same observation has been made before by COMROE and SCHMIDT[4] that certain conditions occur, in which the respiratory centre remains insensitive even to high CO_2-pressures, and can only be influenced by the O_2-supply. Further, BEECHER and MOYER[5] thoroughly investigated these conditions during evipal and pentothal anæsthesia. Such states could indeed be thought of as militating against the Reaction Theory, but of course, still more so against the CO_2-regulation Theory. We shall only be able to attempt an explanation after a study of the effect of chemoreceptors.

A quite remarkable observation is that of COMROE[6], namely that direct injections of $NaHCO_3$-solution, buffered with carbonic acid, into the respiratory centre produced hyperpnœa in 42% of the cases, while corresponding injection of acid produced the same effect in only 3·8%. This observation would favour the CO_2-

[1] KL. GOLLWITZER-MEIER, Bioch. Z. *151*, 54 (1924).

[2] J. B. S. HALDANE, G. C. LINDES, R. HILTON, and F. R. FRASER, J. Physiol. *65*, 412 (1928).

[3] J. M. VERSTAETEN, Arch. Int. Pharmacod. *77*, 52 (1948) (containing the older bibliography).

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

[2] E. OPITZ, Ergebn. Physiol. *44*, 315 (1941).

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

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

[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).

[6] J. H. COMROE jr., Amer. J. Physiol. *139*, 490 (1939).

regulation Theory at the expense of the Reaction Theory, if it were not for the fact that injection of free carbonic acid in Ringer's solution had shown itself to be just as ineffective as other acids. The author himself has made no attempt to explain these experimental results.

The *discovery of chemoreceptors* in the *aorta* by HEYMANS and HEYMANS[1] in 1925, and in the *sinus caroticus* by C. HEYMANS and his coworkers[2] in 1930 brought about a complete reorientation of our views about respiratory regulation. On account of this an extensive reshaping of the Reaction Theory became essential. The very extensive literature on chemoreceptors cannot be discussed here, and the reader is referred to the summarizing reports of C. HEYMANS and coworkers[3], CORDIER and HEYMANS[4], HEYMANS and BOUCKAERT[5], GESELL[6], SCHMIDT and COMROE[7], and BOUCKAERT and coworkers[8].

The idea of a peripheral, indeed pulmonary origin for the respiratory excitatory effect of CO_2, is quite old, and lately PI-SUNER and his coworkers (reviewed in PI-SUNER[9]) have attempted to confirm this conception experimentally. Their work, however, has found no recognition.

The general results of the above-mentioned researches may be summarized as follows:—the nerve fibres leaving the *"branchiogenic" zone* of the *glomus caroticum* and the *glomus aorticum* (that is to say the *nervus caroticus* or HERING's nerve, and the *nervus aorticus* or CYON's nerve) play a leading part in the chemical regulation of breathing. (The morphological literature on the subject has been summarized by PALME[10] and GERNANDT[11].) Hæmatogenically produced increase of CO_2-tension or C_H gives rise to be the well-known accentuation of respiratory movements by direct action on the centres and also reflexly through the chemoreceptors. In opposition to this stands the almost certain fact that hyperpnœa due to O_2-lack, which had hitherto been considered as centrogenic is brought about *exclusively* reflexly by chemoreceptors, especially those of the glomus caroticum. After elimination of all chemoreceptors, this hyperpnœa can be observed no longer (see particularly BOUCKAERT and coworkers[12]).

A short communication of DECHARNEUX[1] has been chiefly responsible for the idea that such results are, perhaps, only obtainable under anæsthesia, and that the normal respiratory centre possesses a direct sensitivity to oxygen. DECHARNEUX observed in dogs whose chemoreceptors had previously been removed that there was a slight reduction in the CO_2-content of the blood during the first day at a height of 2389 m. This experiment does not seem to be at all conclusive. The author only states that the carotid and aortic nerves had been removed in these experimental animals. It is well known that the aortic nerves in the dog run together with the nervi vago-sympathici in a common sheath. The branch (going to the nervus laryngicus), which corresponds to the aortic nerve, can indeed be isolated for a short distance and severed, after the sheath has been opened. However, it is not known whether all chemoreceptor fibres are contained in it. Even in the rabbit, where CYON's nerve runs in a completely isolated fashion, we know that a portion of the pressor and chemoreceptor fibres go not through it, but through the vagus nerve (WRIGHT[2]). The author also says nothing about control experiments, whether the sensitivity to O_2-lack had vanished *during anæsthesia*. Finally, hyperpnœa was not directly observed but only assumed on account of a small decrease of the blood CO_2. But such a decrease occurs also with an adequate O_2-supply and without increase of breathing under the influence of rarification of the atmosphere, because the CO_2 is more rapidly excreted under these conditions (WINTERSTEIN and INAY[3]). So there is neither proof of complete elimination of the chemoreceptors nor of a real hyperpnœa due to O_2-lack.

MOYER and BEECHER[4] found a hyperpnœa due to O_2-lack in dogs under very light evipal, pentothal, and cyclopropane anæsthesia after elimination of the vagi and the denervation of the glomus region. A slight increase of narcosis, however, was sufficient to make the hyperpnœa disappear. It differed from hypoxic hyperpnœa of normal animals by a long latent period and was often accompanied by general phenomena of excitation, observations indicating strongly that secondary factors are playing their part. BOUCKAERT and coworkers[1] too had observed in unnarcotized dogs excited states accompanied by temporary increases in respiratory volume, which they described as "psychic".

DAVENPORT and coworkers[5] used dogs, whose aortic and carotid chemoreceptors had previously been eliminated by the operative procedures described by WATT and coworkers[6]. The authors observed during anoxia an initial and transitory phase of reduced tidal air and minute volume followed by an increase of respiratory rate leading to a more marked and protracted elevation of minute volume, persisting when the dogs were again permitted to breathe air. The authors concluded "that the respiration in the anoxæmic deafferented dogs is the resultant of two antagonistic coexistent factors, a central depression and a central stimulation. The minute volume of the respiration represents the algebraic sum of these effects". The central stimulation seemed to be of

[1] J. F. HEYMANS and C. HEYMANS, C. R. Soc. Biol. *92*, 1335 (1925).
[2] C. HEYMANS, J. J. BOUCKAERT, and L. DAUTREBANDE, Arch. int. Pharmacod. Thér. *39*, 400 (1930).
[3] C. HEYMANS, J. J. BOUCKAERT, and P. REGNIERS, *Le sinus carotidien* (Doin & Cie, Paris 1933).
[4] D. CORDIER and C. HEYMANS, *Le centre respiratoire* (Hermann & Cie, Paris 1935).
[5] C. HEYMANS and J. J. BOUCKAERT, Ergebn. Physiol. *41*, 28 (1939).
[6] R. GESELL, Ergebn. Physiol. *43*, 477 (1940).
[7] C. F. SCHMIDT and J. H. COMROE jr., Physiol. Reviews *20*, 115 (1940).
[8] J. J. BOUCKAERT, K. S. GRIMSON, C. HEYMANS, and A. SAMAAN, Arch. int. Pharmacod. Thér. *65*, 63 (1941).
[9] A. PI-SUNER, Physiol. Reviews *27*, 1 (1947).
[10] F. PALME, Z. exp. Med. *113*, 415 (1943).
[11] E. GERNANDT, Acta physiol. Scand. *11*, Suppl. *35* (1946).
[12] J. J. BOUCKAERT, K. S. GRIMSON, C. HEYMANS, and A. SAMAAN, Arch. Int. Pharmacod. Thér. *65*, 63 (1941).

[1] G. DECHARNEUX, C. R. Soc. Biol. *116*, 352 (1934).
[2] S. WRIGHT, Quart. J. Exp. Physiol. *24*, 169 (1934).
[3] H. WINTERSTEIN, Acta aerophysiol. *1*; 3 (1934). – H. WINTERSTEIN and M. INAY, Rev. Faculté Sci., Univ. Istanbul *7*, 41 (1942).
[4] C. A. MOYER and H. K. BEECHER, Amer. J. Physiol. *136*, 13 (1942).
[5] H. W. DAVENPORT, G. BREWER, A. H. CHAMBERS, and S. GOLDSCHMIDT, Amer. J. Physiol. *148*, 406 (1948).
[6] J. G. WATT, P. R. DUMKE, and J. H. COMROE jr., Amer. J. Physiol. *118*, 610 (1943).

chemical origine precluding carbon dioxide as the responsible agent.

On the other hand, the decerebrated cats used by BOUCKAERT and coworkers[1] showed no hypoxic hyperpnœa, just as was the case in the permanently denervated unanæsthetized cats and rabbits used by WRIGHT[1].

So it may be that in higher animals under these abnormal conditions a secondary factor plays a role in the respiratory regulation. This factor, easely to be abolished by narcosis, may be connected with the activity of the brain cortex.

(To be continued)

[1] J. J. BOUCKAERT, K. S. GRIMSON, C. HEYMANS, and A. SAMAAN, Arch. Int. Pharmacod. Thér. *65*, 63 (1941).

[1] S. WRIGHT, Quart. J. Exp. Physiol. *24*, 169 (1934).

Die Assoziation von Radiolarienhornsteinen mit ophiolithischen Erstarrungsgesteinen als petrogenetisches Problem

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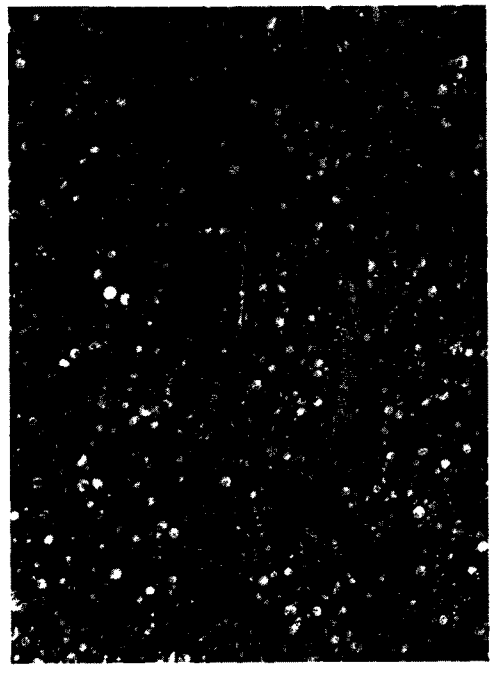
In den Kettengebirgen, die das Mittelmeer umgeben, und in vielen andern jungen und alten Gebirgszügen treten zwei grundverschiedene und eigenartige Gesteinsgruppen in der Regel zusammen auf: kieselige Sedimente, die reichlich Radiolarien enthalten, und eine Gefolgschaft von verschiedenartigen Eruptivgesteinen, die während der Ablagerung der kieseligen Schichtgesteine erstarrt sind und unter denen kieselsäurearme Typen vorherrschen; es sind dies die sog. Ophiolithe. Radiolarienreiche Gesteine treten in den Schichtfolgen der Erdkruste eher selten auf. Sie sind jeweils auf bestimmte Formationen beschränkt. Im alpinen Raum trifft man sie hauptsächlich im obern Jura an, und sie sind hier mit Ophiolithen vergesellschaftet, wie besonders eindrücklich die Aufschlüsse im Oberhalbstein zeigen (GEIGER[2], VUAGNAT[3]). Eine analoge Kombination von Radiolarienhornsteinen und Ophiolithen baut die Danau-Formation Borneos auf, mit der sich der Verfasser beschäftigte und die ihn veranlaßt hat, sich mit der Genese derartiger Assoziationen auf allgemeiner Basis auseinanderzusetzen. Die Entstehung der radiolarienreichen Meeresablagerungen und ihr Verhältnis zu den vergesellschafteten und gleichaltrigen magmatischen Gesteinen bildet in der Tat ein interessantes Problem, das die Biologie, Hydrologie, Geologie und Petrographie in gleicher Weise berührt und uns Gelegenheit gibt, die Resultate verschiedener naturwissenschaftlicher Disziplinen miteinander in Beziehung zu bringen. Zum Ausgangspunkt der Diskussion seien die Organismen, die Radiolarien gewählt.

Radiolarien sind marine Protozoen mit Kieselgerüsten. Diese Kieselgerüste sind auch in Meeresablagerungen der geologischen Vergangenheit gefunden worden, und zwar zuerst in der Radiolarienerde von Barbados, später in vielen andern Formationen. Radiolarien dienen nicht als Leitfossilien; aber sie geben dem Geologen wertvolle Anhaltspunkte über die Bildungsweise der Sedimente, in denen sie auftreten.

Die Radiolarien sind typische und meist die einzigen Fossilien der Hornsteine und anderer kieseliger Sedimente; sie treten aber auch in Tonen, Mergeln, Tuffen und sogar in Erzanreicherungen auf. Manche Hornsteine sind ganz erfüllt von Radiolarienresten; sie werden deshalb als Radiolarienhornsteine oder kurz als Radiolarite bezeichnet (s. Abbildung).

Die meisten der dichten und harten Kieselgesteine sind vor der Entdeckung der in ihnen erhaltenen Radiolarienreste für vulkanische oder metamorphe Bil-



Hornstein der Danau-Formation von Britisch-Nord-Borneo, erfüllt von Radiolarienresten, mit einigen Kalzitäderchen. Vergrößerung 16 fach.

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[2] TH. GEIGER, Beitr. Geol. Karte d. Schweiz, Geotechn. Ser. Lief. 27, (1948).

[3] M. VUAGNAT, Schweiz. min. petr. Mitt. *28*, 263 (1948).