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THE REGULATION OF THE RESPIRATORY MOVEMENTS BY PERIPHERAL CHEMO-RECEPTORS

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1. The regulation of the respiratory movements by chemical influences on the respiratory centers has been demonstrated repeatedly since the classical observations of Rosenthal (1880) on the respiratory effects of oxygen-lack; of Pflüger (1868) on the influence of metabolites accumulated in the blood; and of Hermann (1870) on the action of carbon dioxide and the variations in excitability of the centers which depend upon the oxygen tension of the blood. Of particular importance are the experiments of Fredericq (1890), using for the first time the method of crossed circulation, and the more recent work of Haldane and Priestley (1905), Haldane and Poulton (1909), Henderson (1908–38), Winterstein (1911), Hasselbalch (1912), Hooker, Wilson and Connett (1917), Gesell (1925), Dautrebande (1930), Winterstein and Frühling (1934), and many others. The increase in the concentration of carbon dioxide in the alveolar air, in the blood and in the cells themselves which form these centers stimulates the pulmonary ventilation.

This action of carbon dioxide, or of oxygen-lack, on the various types of respiration in air or in water is found in the most diverse species of animals. It represents a universal biological phenomenon. It is evident in mammals, birds, amphibia and reptiles. Westerlund (1906), Olthoff (1936) and Powers and Clark (1942) observed it in fishes; Fox and Johnson (1934), Peters (1938) and Lindroth (1938) in crustacea; Winterstein (1925) in certain cephalopods, etc. It is interesting to point out that in aquatic respiration a low oxygen tension is more effective than the concentration of carbon dioxide in increasing the respiration (Meyer, 1935; Heerdt and Krijgsman, 1939) an effect which is not surprising considering the physical conditions of the medium. These important questions have been examined by Krogh (1941).

The control of pulmonary or branchial ventilation occurs through the action of the centers which are affected by the gas content of the internal environment in relation to the composition of the external environment. But the possibility of peripheral chemo-receptors which may evoke reflexes adequate for the respiratory needs must also be considered.

"For various reasons," I wrote in 1918, "we consider that in *addition to the central chemical influences* there must be a peripheral regulatory factor acting through receptors which are also sensitive to chemical changes. Just as the vagus transmits afferent impulses in response to mechanical stimuli at the level of the lung which have reflex effects, so there must be pheripheral receptors which are excited by variations in the concentration of carbon dioxide."

This hypothesis has classical antecedents. Donders (1853), Berns (1870) and Traube (1871) thought that the increase of carbon dioxide in the air contained in the lungs must be concerned in the regulation of the respiratory movements.

Nevertheless, because of the lack of sufficient experimental proof, because of the study of the mechanical reflexes begun by Hering and Breuer (1868) and continued by Gad (1880), Zuntz and Geppert (1888), Head (1889) and many others, and because of the very important work of Haldane and his school and of those previously mentioned on the effect of the gas content of the blood on the functions of the respiratory centers which regulate the movements, no attention was paid to the peripheral chemical control of the respiration.

Starling stated in his *Principles of Human Physiology* (1915): "If . . . we succeed in altering the tensions of the two gases (oxygen and carbon dioxide) in the alveolar air we may assume that the tensions of the gases in the arterial blood leaving the lungs are altered in the same ratio." Through the action of chemoreceptors in the terminal portions of the respiratory apparatus, the composition of the alveolar air and therefore of the gas content of the blood is adjusted with the result that the ventilation would always be what the circumstances require. Only high concentrations of carbon dioxide in the inspired air, which increase the ventilation enormously, are able to raise the concentration of carbon dioxide in the alveolar air appreciably. The great speed of the responses, and the exactitude with which compensation is produced, lead one to suppose that there are reflexes evoked by chemical excitation from the respiratory apparatus which would operate previous to any humoral influence.

The experiments of Haldane (1922) show that if air with increasing quantities of carbon dioxide is breathed, it is possible for the ventilation rate to be doubled with practically no change in the composition of the alveolar air. Campbell, Douglas and Hobson (1914) observed that an increase of 2.5 mm. Hg in the carbon dioxide tension is sufficient to bring the ventilation to 10 liters per minute. These observations have been confirmed repeatedly (Campbell, Douglas, Haldane and Hobson, 1913; Douglas and Harvard, 1932; Barcroft and Margaria, 1931).

Nor, on the other hand, does rarefaction of the air change the gas content of the arterial blood appreciably, as has been known since the work of Fränkel and Geppert (1883): at a pressure of 410 mm. Hg there is no change in the gas content of the blood; nevertheless the respiratory dynamics have been modified.

The results obtained by Scott (1908) furnish very interesting data: without the vagi, the control of the respiration is uncertain, the reactions are slower and last longer after a carbon dioxide mixture has been breathed, and in general the adjustment of the respiration to physiological requirements is inexact. If the respiratory movements depended solely upon the humoral influence on the centers, and the vagus were limited to the rôle of a sensory nerve for mechanical receptors, there would not be such marked differences in the respiratory reactions to inspired carbon dioxide when the vagus is intact and when it has been cut. Our experiments designed to clarify this problem have been numerous and of various types.

At first we studied (1918) the behavior of the respiration in vagotomized dogs exposed to the same concentrations of carbon dioxide in air, before and after the operation. Observations were made immediately after the section of the vagi or some hours later. The differences with respect to the normal were always

noteworthy in that they showed lack of precision and delay in motor reactions when the vagal innervation was absent. Our conclusions were: 1. The constancy of the proportion of CO_2 in the alveolar air contradicts the hypothesis that the respiratory stimulation is exclusively of central origin evoked by the excess of CO_2 or lack of O_2 in the blood. 2. The lung and the bronchial ramifications are sensitive to different chemical stimuli, which can evoke reflexes. 3. In addition to the well known action on the respiratory centers, there is exerted a parallel or perhaps a previous peripheral influence due to the excitation of end-organs which are sensitive to stimuli of chemical nature by the CO_2 contained in the inspired air.

The following year in collaboration with Bellido (1919–21) and as a more evident demonstration we devised a crossed-circulation technique, otherwise known as the "dog with two heads." The central stumps of the carotids and jugulars of the donor dog "A" are joined to the cephalic stumps of the corresponding vessels of "B," the dog in which the experiment is performed. The vertebral arteries of the latter dog are also ligated, and the animals are chosen so that "A" is sufficiently larger than "B" and its carotid pressure higher, thus preventing the head of the recipient from receiving its own blood through the intravertebral plexuses. C. Heymans and Ladon in 1925 and J. F. and C. Heymans in 1926 proposed a definitive method similar to ours except that they cut off the head of "B" (method of the isolated head) and record respiratory movements of the larynx and floor of the mouth. With Puche (1930) we studied various ways of registering these movements with the purpose of improving the recording. Isolation of the head assures that only the blood of the donor dog reaches it, because it is connected to the trunk only by the vagi.

When the respiratory centers of "B" are perfused by either of the two procedures with the blood of "A," which is breathing normally or in some of the experiments is given artificial respiration, and "B" or its trunk which has been separated from the head is made to breathe air with CO_2, an increase in the frequency and depth of respiration is observed.

With Puche and Raventós (1930) we used also the technique of the isolated head. As in our first experiments of 1919 and succeeding years, if after decapitating "B," leaving the head which is connected with the trunk only by way of the vagi, we caused the trunk to breathe air with CO_2, the head responded with an increased intensity of the respiratory movements, despite the fact that it was being perfused with normal arterial blood from the donor dog "A."

The researches of J. F. and C. Heymans (1926–28) showed that the head, besides responding to mechanical stimulation of the pulmonary vagal endings (Hering-Breuer reflex), also responds to peripheral chemical stimuli. A reflex apnea is produced by over-ventilation as described by Hering and Breuer (1868) and afterwards studied by Baglioni (1903), Foa (1909–11), Githens and Meltzer (1914), Joseph (1922), Puche (1923), Meek (1923) and others. This apnea has been generally attributed to over-distention of the lungs, but Heymans and Heymans state that the major factor in producing it is the peripheral sensitivity to the concentration of CO_2 in the blood. Such a sensitivity was suggested by

Luciani (1888) and Bordoni (1888). Anemia of the trunk with asphyxia of the tissues causes acceleration of breathing, thus confirming the possible peripheral origin of the dyspnea in addition to its central origin, a thesis which had been proposed earlier by Francois Franck (1890), Hoffmann (1900), Porter and Newburgh (1916–17) and Dunn (1920). Heymans and Heymans were able to demonstrate also the relation between the cardio-aortic pressure and the breath rhythm, and, a fact which interests us particularly, respiratory responses to changes in the composition of the inspired air and in the gas content of the blood circulating through the heart and great vessels.

Heymans, Bouckaert and Regniers (1933) write: "J. F. and C. Heymans observed that intense hyperventilation of the trunk of dog 'B' causes reflex apnea of the isolated head of the same animal; on the other hand, progressive asphyxia of the trunk by withholding artificial respiration *or the administration of air with carbon dioxide*, causes the reappearance of respiratory movements of the head followed by a progressive increase in their amplitude as the asphyxia becomes more severe." Heymans and Heymans wrote in 1927: "These experiments taken together show that the vagi contribute to the reflex regulation of the activity of the respiratory center according to the peripheral respiratory and circulatory conditions. The respiratory center can be excited in the same way by a peripheral state of asphyxia or anoxemia as by a central state." Having demonstrated the existence of respiratory reflexes evoked by chemical stimuli Heymans and Heymans (1927) then set out to discover the peripheral origin of the respiratory tone and of the vagal influence on the respiration. For this purpose they performed various series of experiments demonstrating that the cardio-aortic intraceptive zone is the place of origin not only of circulatory reflexes but of respiratory reflexes as well and that the stimuli can be chemical as well as mechanical. "The intrapulmonary or humoral accumulation of carbon dioxide in the trunk constitutes the vagal reflex stimulus of the respiratory center of the isolated head."

From their experiments Heymans and Heymans concluded that the respiratory reflexogenic zones which are affected by chemical stimuli are found in the central organs of the circulation, the heart and the aorta, and that the lungs have no specific excitability to carbon dioxide. In our judgment this last proposition has not been confirmed. In the first place it should be remembered that it is more or less asphyctic blood circulating through the lungs which is used as a stimulus and *not the inspired air*, which would affect the whole respiratory tree, from the nose to the pulmonary alveoli. Thus it is rather the functions of a reflexogenic zone in the circulatory apparatus which are being investigated—the sensory innervation of the pulmonary vessels *stimulated by changes in the composition of the blood*—and not whether the respiratory pathways respond to the composition of the air. Again, the important operative intervention, extirpation of the heart and great vessels, may suffice to put the animal in an unphysiological state; and one must reckon also with the possibility that many sensory fibres of the pulmonary plexuses which pass to the vagi may be damaged by the same operation. All of this may damage or alter the vagal sensitivity and cause the vagotonic type of respira-

tion observed and the scarcely appreciable reaction to the circulation of the hypercapnic blood. It is invalid to argue that the Hering-Breuer reflex, which is known to be very rough, is still present. Anrep and Samaan (1933) have shown in denervation experiments that a very few remaining fibres are sufficient to cause this reflex to persist.

After the demonstration by Heymans and Heymans of the existence of circulatory reflexogenic zones with chemo-receptors we decided to return to the subject of pulmonary sensitivity. In new publications with Puche (1930) and with Raventós (1931–33) we employed the technique of the isolated head as usual, and in order to exclude all circulatory influence we bled the trunk "B" completely and rapidly by cutting the abdominal aorta until the heart stopped. Thus all circulatory factors both mechanical and chemical are suppressed since the blood no longer circulated. It is certain that with this bleeding the sensitivity of the lungs is diminished; but this fact, which furnishes a valid objection to negative interpretations, is favorable the other way around; in the normal state the reflex would logically be more intense and more effective.

With the addition of CO_2 in varying proportions to the air going into the trunk, while identical mechanical conditions of respiration are maintained, it is shown that even in such unfavorable circumstances the inhalation of CO_2 intensifies the movements of the isolated head which are already increased as a result of hemorrhage and subsequent asphyxia of the tissues.

We have tested also the response to the inhalation of irritant gases, hydrogen chloride and ammonia, and confirmed the observations made with Bellido (1919).

Heymans has (1929–33) raised the objection to the conclusions from these experiments that in the production of the reflexes observed it is not a specific sensitivity which is acting, but the general sensitivity to irritant agents. "The results obtained by Pi-Suñer and Bellido," state Cordier and Heymans (1935) "are certainly due to the fact that these authors have administered by inhalation air with concentrations of CO_2 which pass beyond physiological limits and even beyond the pathological. It is a question of phenomena of pharmacological order." It is difficult to know where a specific chemical excitation ends and where an irritant, nociceptive excitation of chemical origin begins, and where is located the boundary which separates physiology from pharmacology. HCl and NH_4OH for example do not increase the depth and rate of respiration like CO_2, but they inhibit it or provoke abnormal reactions: cough, spasm, etc. Barcroft and Margaria (1932) observed that high concentrations of CO_2 cause a characteristic type of respiration, which is not a simple increase but may be faster or slower depending upon the previous rate. After section of the vagi the breathing of high concentrations of CO_2 in air is usually followed by completely abnormal symptoms analogous to those observed by Lumsden (1923) upon sectioning the medulla at various levels, and similar to those which Taylor (1930) observed after the administration of cyanide: apneusis, gasps and finally paralysis. Some of our positive results have been obtained with mixtures of air and CO_2 which are closer to the normal and in which it cannot be said that carbon dioxide acts as an irritant gas.

The negative results of Partridge (1933), who attempted to record vagal action currents using inspired CO_2 as a stimulus, have also been cited in opposition to the theory of pulmonary chemical sensitivity. This is a problem which we began to study with Bellido in 1921. The electrovagograms which we obtained then showed certain differences when the animal breathed carbon dioxide, but were not conclusive. Our technique at that time was deficient. Adrian (1933) states that concentrations of CO_2 in air higher than ten per cent cause a modification, a slight diminution in the intensity of the impulses passing in the vagus when the lung is distended, but that these effects are small and within the limits of possible experimental error. Bullring and Whitteridge (1943–44) say that an increase in vagal electric discharge—single fibre preparation—occurs as soon as a volatile anesthetic—ethyl chloride, chloroform, ether, divinyl ether, trichlorethylene, etc.—reaches the lung, whether it is administered by inhalation or intravenously. But it is not possible to state that the respiration of air with carbon dioxide in greater concentration than normal is accompanied by definite signs in the electrovagogram.

In a later series of experiments (Pi-Suñer and Raventós, 1931) we have returned to the question, making the conditions of observation more rigorous even at the cost of simplicity. Using the method of the isolated head, we placed a cannula in the pulmonary artery and another in the left auricle of the trunk of "B." All of the rest of the heart and the thoracic aorta were removed, care being taken to avoid damage insofar as possible to the nerve fibres which form the plexuses at the roots of the lungs and their vagal continuation. Defibrinated, oxygenated, blood was perfused through the lungs by means of a Dale Schuster pump. Thus only the lungs and head of dog "B" remained alive, connected by the vagi which had been cut below the heart. After this procedure it is still possible to obtain respiratory responses to the inhalation of air with CO_2. It is evident that such reflexes cannot originate in the heart and aorta which are no longer present, and that they are due to the influence of the inspired carbon dioxide upon lungs which are perfused with blood of constant gas content.

Another series of experiments recently completed (1938–42) consisted in denervating the heart and great vessels while leaving the pulmonary innervation intact insofar as possible. Again we used the technique of the isolated head perfused with blood from a donor dog "A." Relying upon the anatomical findings of Lim (1893), Cannon, Lewis and Britton (1926) and Barry (1935), we established a technique of intrathoracic denervation of the heart similar to that described by Anrep and Samaan (1933) and Anrep, Pascual and Rossler (1932).

With this procedure the breathing of air with CO_2 by the trunk gives rise to changes in the respiratory movements of the head. Now the responses to chemical stimuli cannot arise in the heart and aorta which have been denervated, nor from the carotid sinus which, as in all the experiments with the isolated head, remains in the head and is perfused by blood from the donor dog.

It is important to mention the work of Dirken and Van Dishoeck (1937) who also demonstrated the sensitivity of the lung to changes in the concentration of CO_2 in the alveolar air and concluded that the nerve endings present in the lungs

are sensitive to changes in the concentration of CO_2 such as are found normally in alveolar air, i.e., 5 to 6 per cent.

Dirken and Van Dishoeck consider furthermore that the sensitivity of the pulmonary receptors is limited to CO_2 because they did not note any difference in the reflex respiratory responses, when the proportions of oxygen and nitrogen were varied in the breathed gas mixtures. Bilateral section of the vagi abolished the reflex effects of changes of CO_2 in the air.

After confirming the sensitivity to CO_2 of pulmonary and bronchial chemo-receptors, the authors reach a paradoxical conclusion: these receptors are not the instruments of the normal regulation of the respiratory movements. They observed in some experiments that as the frequency of the inspirations increased their amplitude was reduced, and they inferred from this fact that the ventilation was not changed. They doubt that the phenomena observed depend upon a direct sensitivity to carbon dioxide on the part of the pulmonary endings, attributing them rather to changes in the excitability of the receptors for their natural physiological stimulus: the collapse and the expansion of the lung evoking reflexes through mechanical stimuli. However the fundamental fact is the existence of endings which are sensitive to changes in the concentration of CO_2 in the alveolar and bronchial air and which influence the movements of respiration.

Recently Hammouda, Samaan and Wilson (1942–43) reaffirmed once again that the fibres in the vagi which conduct the afferent impulses of the reflexes of inflation and deflation are of pulmonary origin, and Bagoury and Samaan (1941) have studied respiratory reflexes by injecting ketone-bodies into the pulmonary circulation. The authors prevented any possible central action of the blood; the vagal excitation arose from sensory endings of the lungs. These pulmonary endings would therefore be sensitive both to mechanical and to chemical stimuli.

Eppinger, Papp and Schwartz (1924) infer the mediation of pulmonary chemical sensitivity in studying the mechanism of cardiac asthma; Dunn (1920) and Binger and Moore (1927) consider also local pulmonary influences when they attempt to interpret the hyperpnea of pulmonary embolism, and Churchill and Cope (1929) do likewise in considering the dyspnea observed in pulmonary edema and which they attribute to the excitation of sensory endings in the lung.

Another important aspect is the debated intervention of the lung in the maintenance of vagal tone. Heymans and Heymans observe a disappearance of the respiratory tone, maintained by the vagus, when the stimuli arising in the heart and aorta are no longer present and only those arising in the lungs remain. Heymans and Heymans conclude that the lungs are not the site of origin of the centripetal vagal impulses which maintain the physiological respiratory vagal tone and the reflex excitation and inhibition of the respiratory center in relation to respiratory and circulatory mechanisms.

Our observations demonstrated that after bleeding the trunk and therefore excluding all circulatory influence either mechanical or chemical, the normal rhythm of the respiratory movements of the head continues. *It is only after section of the vagi that respiration of the post-vagotonic type appears.* This suggests

that at least the sensory innervation of the lung assists in maintaining the vagal tone.

The latter proposition is confirmed by the investigations of Anrep and Samaan (1933). These authors cite the work of Pavlov (1895–96) and his pupils and collaborators, Cachovsky (1899) and Cheshcov (1902), studying the respiratory movements in vagotomized dogs surviving up to nineteen months after operation. Just as in the acute experiments, the rate is reduced to 4–8 per minute immediately after the section of the vagi, speeding up in the second or third week, and slowing down again to the same original bardypneic rate which is maintained until the death of the animal. Pavlov attributed the initial slowing to the cutting of sensory fibres of pulmonary origin and the subsequent acceleration to a process of irritation in the same fibres with scarring of the central stump of the cut nerve. When the process of cicatrization is completed the rhythm characteristic of the absence of vagal afferent impulses is re-established. Sharpey-Schafer (1932) states that the respiratory slowing is due to the increased resistance to the passage of air through the respiratory pathways owing to paralysis of the laryngeal nerves. It has not been difficult to demonstrate the error of this opinion. Heymans and Heymans (1927) assert that the post-vagotonic rhythm is due to the lack of cardio-aortic control. The "respiratory tone" is of cardio-aortic origin and disappears when the vagal fibres arising in that region are cut. "No direct evidence in support of this view is, however, provided," write Anrep and Samaan, who have shown that section of the vagal fibres at the level of the root of the lung does not alter the cardio-aortic innervation and that the branches which leave below this point go to the lung, with the exception of a few which pass to the esophagus. Taking into account these anatomical findings, Anrep and Samaan (1933) denervated the heart and aorta by means of intrathoracic dissection without producing the respiratory rhythm typical of vagal section. The section of one of the vagi and cardio-aortic denervation on the opposite side did not cause vagotonic respiration either. Later section of the remaining vagus in the neck caused this type of respiration to appear at once. Moreover, they sectioned the vagus below or at the level where the pulmonary branches leave the main trunk and compared the different results in the two cases. With the low section no differences in rate were observed; with the high section the characteristic slow respiration appeared; it switched from 24 to 7 respirations per minute. Subsequent bilateral vagotomy in the neck no longer modified this slow rate. This observation produces additional evidence against the cardio-aortic theory as well as against the laryngeal theory of Sharpey-Schafer.

Bouckaert and Heymans (1933) comment: "The reflex and tonic influences of the pulmonary vagus on the activity of the respiratory centre is a well-known and generally accepted fact (Hering and Breuer, 1868; Head, 1889; Haldane, 1922; J. F. and C. Heymans, 1926; C. Heymans, 1928; Hoffmann and Keller, 1929; Hess, 1931; Anrep and Samaan, 1933). It has been shown by J. F. and C. Heymans (1926) and C. Heymans (1928, 1929a, b) that the vago-depressor nerves in dogs are also the centripetal paths of respiratory reflexes in relation with the

cardio-aortic blood-pressure .... The normal arterial pressure in the left heart and aortic arch maintains a respiratory reflex tonus. Anrep and Samaan (1933) cannot find any evidence that cardio-aortic impulses invariably exert on the rate of the respiration a regulating influence which can be compared with the definite and constant dependence of the respiration rate on the pulmonary innervation.

Recently Sidney Harris (1945) has studied the behavior of the respiratory tonus in anoxia. During the reduction of oxygen content in inspired air to about 8 per cent the volume of the cat's chest at the end of expiration increased about three times the volume of a normal respiration. After vagotomy the anoxic increase in expiratory volume was about one-third as great as with the vagi intact. Crushing the nerves from the carotid chemo-receptors had little or no effect upon the reaction. An excess of the CO_2 in the oxygen deficient air did not prevent the increase in respiratory chest volume, but it did greatly increase the minute-volume of respiration. Gesell and Moyer (1934–35) and Green and Swanson (1938) had earlier reached similar conclusions.

Hermann, Jourdan and Vial (1934) suggest as a result of their experimental observations that the tone of the pulmonary vagus is continuous, depressing the activity of the cardio-inhibitory center and eliciting circulatory pressor reflexes which are antagonistic to the depressor reflexes arising in the cardio-aortic sensory area and in the sensory area of the carotid sinus. These conclusions, perhaps too schematic, are nevertheless of interest because they are based on experiments which demonstrate once again the rôle of the pulmonary vagus in controlling the respiratory tonus.

The existence of sensory endings in the respiratory apparatus should now be considered. Schumacher (1902), Hudovernig (1907), Tello (1924), Perman (1924), Gaylor (1934), demonstrated these receptors in the alveolar duct and the presence of fibres of pulmonary origin in the vagus nerve. Larsell (1921–39), Larsell and Burget (1924) and Sunder-Plassmann (1933) describe sensory nerve endings in the mucosa of the bronchi and trachea which are probably sensitive to mechanical stimuli. According to Larsell (1939), receptors of a different morphological type are found in the depths of the respiratory tree and it may be inferred that they are chemo-receptors because of their location directly in the air passage.

The fibres proceeding from all these endings ascend with the vagus, but Beccari (1934) believes that some afferent respiratory fibres also pass with the sympathetic, a fact in accord with the scheme of double sensory innervation of the vegetative organs through the sympathetic and parasympathetic outlined by Pi-Suñer and Puche (1928–30). Brookhart and Steffensen (1936) observe respiratory effects when the stellated ganglion is ablated, but they do not conclude that the afferent fibres implicated in the Hering and Breuer's reflex should necessarily pass through it.

Numerous facts, established by us and by other authors, demonstrate the chemical sensitivity of pulmonary origin. Heymans and Heymans have shown that the cardio-aortic areas are sensitive to chemical stimuli, and they think that the latter sensitivity is linked to the circulatory apparatus and excludes the

pulmonary chemical one. We consider, however, that no incompatibility exists; that, on the contrary, the effects of peripheral excitation of separate origin support each other functionally.

II. It is a well established fact that different sensory regions operate synergistically in the control of distinct vegetative functions. In the case of the respiratory and circulatory reflexes the sensory regions are various and do not hinder the function of one another but rather coordinate their regulatory influences.

Since the early observations of Pagano (1900) and Siciliano (1900) and the description by Hering (1927–32) of the functions of the carotid sinus, a number of authors have devoted themselves to this very important reflexogenic zone. The sinus is concerned not only with the regulation of circulatory dynamics under the influence of changes in the blood pressure, but its action extends also to various functions; among these is the respiratory.

"Many clinicians," write Heymans, Bouckaert and Regniers (1933), "have called attention for some time to the fact that carotid compression elicits changes in respiration." Tschermack (1866), Quincke (1875), Sollmann and Brown (1912), Danielopolu, Asland, Marcou, Proca and Manescu (1927), Daniclopolu, Manescu and Proca (1928), Wenckebach and Winterberg (1927) proved that traction on the cephalic stump of the recently cut carotid awakes reflexes through mechanical excitation of the sinus. Similar findings have since been demonstrated repeatedly: Gollwitzer-Meyer and Schulte (1931), Schmidt (1932), Winder, Winder and Gesell (1933), Gemmill and Reeves (1933).

Moisejeff (1927) demonstrated that such effects originate in the sinus. Upon ligating the vessels which arise from the bifurcation of the carotid and perfusing the sinus he found inhibition of the respiratory movements when the pressure of the perfusing fluid increased. C. Heymans (1929) and Heymans and Bouckaert (1929–30) have confirmed these results. Afferent nerve impulses arise in the carotid sinus as a result of mechanical excitation and intervene in the process of regulation of the respiratory dynamics just as in the case of the circulatory. Houssay and Orias (1934) have studied the effects of excitation of the sinus on the contraction of the smooth muscle of the bronchioles and have observed inconstant reflex effects.

But not only do the mechanical conditions of the circulation influence the respiration through carotid and aortic body reflexes. *The composition of the blood is equally effective*, particularly the content of CO_2 and oxygen.

Heymans, Bouckaert and Dautrebande (1930–31–32) using the previously described technique of Moisejeff, discovered that acapnia of the blood produces reflex inhibition of the respiratory center while blood with an excess of CO_2 stimulates the center. According to Heymans, Bouckaert and Regniers (1933) the most effective chemical stimuli for the carotid body are hypercapnia, anoxemia and increased concentration of hydrogen ions. There immediately appeared numerous confirmations: Owen and Gesell (1931), Schmidt (1932), Selladurai and Wright (1932), Bernthal (1934), Heymans, Bouckaert and Samaan (1935), Gayet, Bennati and Quivy (1935), Samaan and Stella (1935), Zottermann (1935), etc. Slight changes in the composition of the blood passing through the

carotid sinus give rise to vigorous circulatory and respiratory responses. Hill and Flack (1908), Piras (1922), Frey (1923) and Hess (1931) did not believe that the respiration could be influenced normally in reflex fashion by a greater or lesser concentration of CO_2 in the blood. Hering (1932) and Mies (1932) discuss the chemical sensitivity of the carotid body; Gollwitzer-Meyer and Schulte (1931) and Gollwitzer-Meyer (1934) the specificity of the sensitivity to CO_2. Such a mass of confirmatory results was so gathered together that there is no possible doubt.

Anatomical investigation has also been here of great value. De Castro (1926-28) began the studies by describing a complex system of receptors in the carotid sinus. He explored immediately the carotid body or glomus at the bifurcation of the carotids in anatomical continuity with the sinus. It is a small organ which has the appearance of an endocrine gland, possesses certainly an intense metabolism and among its cells is distributed a profuse net of nerve endings. Sunder-Plassmann (1930) furnishes interesting data and Heymans, Bouckaert and Regniers (1933) give in their turn a description of the region. Ask-Upmark (1935) has studied the comparative anatomy of the sinus in twenty-seven species of animals. Nonidez (1935–36) and Boyd (1937) have found glomerular tissue in other vaso-sensory regions: principally in the aorta (Penitschka, 1931)—"Glomus aorticum"—and in the vicinity of the pulmonary artery—"glomus pulmonale." There are other analogous cellular formations, e.g., the coccygeal body. And perhaps one might refer to this group of small organs the groups of cells attached to or near the peripheral vessels described by Goormaghtigh (1935) which he considers to belong to the neuro-vegetative system. The glomera are probably a part of the chromaffin system even though their cells do not usually show the characteristic protoplasmic granules which are stained by chromates. The glomera seem to respond especially to chemical stimuli, above all those which are found in asphyxia: anoxemia, hypercapnia, acidosis.

In 1931 Heymans, Bouckaert and Dautrebande observed that ligature of the nerve fibres arising in the carotid sinus prevents reflex adaptation to changes in the pressure of the blood contained in the sinus but does not abolish the reflexes elicited by chemical stimuli. And reciprocally according to Heymans and Bouckaert (1932) it is possible to inactivate the chemo-receptors by producing emboli with lycopodium powder in the vessels of the glomus while preserving the sensitivity to pressure. Gollwitzer-Meyer and Schulte (1931) and Gollwitzer-Meyer (1934) observed that lobeline exerts its action, which is identical with that of anoxemia, only when it reaches the carotid body. Danielopolu, Asland and Marcou (1933) also separate the location of presso-receptors of the sinus and chemo-receptors which are in the carotid bodies. Camus, Bernard and Merklen (1934) brought new confirmation by cutting the fibres from the presso-receptors, and Comroe and Schmidt (1938) conclude that the receptors for pressure are found particularly if not exclusively in the carotid sinus itself, while the chemo-receptors are at the origin of the occipital artery near the carotid body and probably in the carotid body itself.

The study of the electrical variations produced in the nerve of Hering due to

the functional state of the carotid sinus has given data which demonstrate also the topographical separation of the receptors. Bronk and Stella (1932) observed that action currents in the nerve result not only from distention of the sinus by increase in the blood pressure, but can be produced also by other kinds of stimulation. Heymans and Rijlant (1933) showed the presence of impulses in the same nerve which bore no relation to the pressure in the sinus and were dependent on the state of ventilation of the animal: when the ventilation is poor the discharges are more intense; the excitation which sets up the impulses is not mechanical but chemical depending upon the gas content of the blood. Bogue and Stella (1934–35), Zottermann (1935), Euler, Liljestrand and Zottermann (1939) confirm these observations in experiments on cats and suppose that the starting point of the impulses is the carotid body. Bronk and Stella (1934) confirm the independence of the chemo-receptors and the presso-receptors. Samaan and Stella (1935) have studied the influence of changes in the composition of the blood on the action currents in the nerve from the carotid body and have shown that these currents cease when the tension of carbon dioxide in the blood is reduced below 32–35 mm. Hg. The physiological tension of carbon dioxide in the arterial blood will maintain therefore a tonic excitation of the carotid chemo-receptors and through them of the respiratory centers as has been shown by Selladurai and Wright (1932) and by Witt, Katz and Kohn (1934). Euler, Liljestrand and Zottermann (1939) agree with the earlier conclusions but consider that the physiological tension of oxygen is equally as effective as that of carbon dioxide.

In the aorta the two types of receptors, mechanical and chemical, are likewise found separated from one another. Comroe (1939) has studied the aortic chemo-receptors and particularly the aortic body which is similar to the carotid body, and has established that the bodies are in both cases the point of origin of circulatory and respiratory responses to anoxia; in the dog the aortic receptors are said to elicit reflexes which are predominantly circulatory while the carotid body is the principal point of origin of respiratory reflexes. There are nevertheless individual differences, and in the cat the functional specialization does not seem to be so clear. Gellhorn and Lambert (1939) believe that the circulation is regulated by the presso-receptors while the respiration depends principally on the chemo-receptors.

III. With the demonstration of the chemical sensitivity of the various vascular zones, the most important of which are the carotid sinus and the aorta, it was logical to study the physiological significance of this sensitivity in comparison with that of the respiratory centers. "Central chemical control," writes Gesell (1939) "which had been accepted on faith, was not on the defensive. In the confusion, many adopted new faiths which carried them too far, for luck was with the majority. This they do with the same enthusiasm as their predecessors who thought that the respiratory regulation and also the circulatory was carried out exclusively by the state of the blood supplying the centers." Schmidt and Comroe (1941) state: "For many years the physico-chemical aspects of respiratory control were dominant, but during the past decade the reflex factor has grown

steadily in stature until, in our opinion, the time has come to reverse the traditional attitude".

In making a comparison between the central and the peripheral effect of the chemo-receptors Heymans considered that, at least in the case of anoxemia, the effect of excitation of the sinus takes precedence over that of the centers in the control of the movements of respiration. Heymans, Bouckaert and Dautrebande (1930) observed that as a result of denervation of the vaso-sensory zones, only a moderate acceleration of the rate of respiration and a slight increase in the blood pressure is produced when the dog breathes nitrogen without oxygen, instead of the response of violent hyperpnea and extreme hypertension by the normal animal.

A number of investigators have obtained similar results. Selladurai and Wright (1932), Witt, Katz and Kohn (1934), Euler and Liljestrand (1936), Euler (1938), and Gesell and Lapides (1938) observed that in general respiration is depressed after simple denervation of the carotid sinus. Schmidt (1932) and Gemmill and Reeves (1933), studying the immediate effects of denervation of the sinus, had shown that anoxia does not produce an increase in the pulmonary ventilation, but rather a decrease. Schmidt and Comroe (1940–41) and Moyer and Beecher (1942) agree in the statement that hypoxia increases the respiration of animals whose vaso-sensitive zones have been deafferented. Nevertheless these animals have gone through a long period of depression. Watt, Dumke and Comroe (1943) assert also that anoxia produces stimulation of the vaso-chemo-receptors while it leads primarily to depression of the centers. In experiments in which the denervation had been carried out previously, performed when the animal had recovered from the operation ("chronic" experiments), Gemmill, Geiling and Reeves (1934) observed a slight excitation produced by anoxia, but only when it was not excessive. Wright (1934) in "acute" experiments on anesthetized rabbits and later in chronic experiments confirms the respiratory depression caused by anoxia after carotid denervation. Smyth (1936–37) states that this depression is considerable and, moreover, anoxia reduced the intensity of the response to CO_2 in denervated animals. In the rabbit Stella (1935) does not find significant effects of denervation: the respiration may decrease in depth but increase in rate. Schmidt, Dumke and Dripps (1939–40) have blocked the sinus nerves with procaine and observed scarcely any change from the normal respiration.

Wright (1936) remarks that after denervation of the sinus and bilateral section of the vagi, oxygen-lack does not produce hyperpnea. After the sensory nerves of the carotid sinus and the aorta have been removed Wright finds that severe anoxemia in anesthetized cats instead of causing respiratory activation produces a reduction in the ventilation. The changes in the respiratory gases in the blood are greater in the operated animals than in the normal. He concludes that up to a certain point the vascular receptors in the carotid body and the cardio-aortic area protect the centers from chemical influences "in loco."

Schmidt (1932), Beyne, Gautrelet and Halpern (1933); Winder (1933);

Mulinos (1934); Henderson and Greenberg (1934); Wright (1934–36–38) Gayet, Bennati and Quivy (1935); Brewer (1937), Gesell and Moyer (1937); Smyth (1937); Comroe and Schmidt (1938); Gellhorn and Lambert (1939); etc., agree that anoxemia is the most effective stimulus for the vascular chemo-receptors, particularly of the carotid body.

Bernthal (1938) by perfusing the isolated carotid sinuses with blood of fixed pH and varying the concentration of oxygen, observed that 18 per cent oxygen causes at the most a moderate vaso-dilatation and hypopnea, while 15 per cent oxygen gives rise to vaso-constriction and hyperpnea an effect intensified when the proportion of oxygen is reduced to 12.8 per cent. A drop to an oxygen tension of 10 mm. Hg causes a marked increase in vaso-constriction and respiratory rate.

In spite of these facts, Cromer and Ivy (1931) noted that dogs from which the carotid sinuses had been removed aseptically, work in the treadmill without greater effort than normal dogs and do not show any respiratory disturbances. It should be noted however that in these dogs the cardio-aortic receptors remained intact. Decharneux (1934) also observed adequate respiratory responses afte denervation of the sinus. Dautrebande (1937) stated that dogs with complete deafferentation of the sinus and aorta respond to low atmospheric pressures in the same regular and adequate fashion as do normal dogs. Gesell (1939) cites cases of hyperpnea in response to anoxemia after denervation of the sinus.

It has long been known that the cyanides and sulfides inhibit oxidative processes in the organism. The mechanism of action of cyanides is well-known. Cyanide inhibits cellular oxidations by combining with cytochrome oxidase. Sulfides act in the same manner. A. Pí-Suñer and J. Pí-Suñer (1928–29) affirm that to the extent that the cyanides impede the processes of oxidation, in particular of glucose and fat, they evoke trophic reflexes which produce hyperglycemia and hyperlipemia.

Haggard and Henderson (1922) have studied the effects on the respiratory movements of sodium sulfide injected intravenously. Heymans and Heymans (1927) and Heymans, Bouckaert and Dautrebande (1930) showed, and it was quickly confirmed by Owen and Gesell (1931), that the injection of sulfide or cyanide into the carotid sinus causes very intense respiratory responses. Winder and Winder (1933) examined the action of the sulfides and called attention once more to the strong respiratory reflex effect elicited from the chemo-receptors of the carotid body. Denervation of the sinus modifies the response: doses which were previously extremely effective evoke, after denervation, a very different type of response of slight intensity. In all cases the reactions to stimulation of the sinus are more intense than those obtained by direct application to the centers. Winder, Winder and Gesell (1933) required quantities 25 to 75 times as great after denervation of the sinus to produce occasional respiratory effects. Winder's (1937) statement that monoiodo acetic acid acts upon the carotid body in a similar way as cyanides and sulfides is not in agreement with the general opinion that the first is an inhibitor of sulfhydryl enzymes while cyanide inhibits cytochrome oxidase.

These drugs also act upon the respiratory centers. Winder, Winder and Gesell (1933) applied cyanide directly to the fourth ventricle but noted that the respiratory movements were simulated only by larger doses than those required on the sinus; further increase in the doses caused difficulty of respiration which finally ceased. Injection of sulfides and cyanides into vertebral artery requires larger doses in order to alter the respiratory movements than are required with injection into the sinus.

Another factor which should be kept in mind in considering the action of cyanide or sulfide is the rôle of the vagus. According to Haggard and Henderson (1922) the respiratory effects in these cases are due to the action of the drugs on the vagal endings of the lung, in view of the differences in the responses depending on whether one is dealing with intact or with vagotomized animals.

Winder (1937), Bernthal and Weeks (1939) arrived at the conclusion that changes in pH in the blood and in the sensitive cells are a prime factor in normal carotid body stimulation, and Von Euler, Liljestrand and Zottermann (1939–41) confirm that intracellular acidity in the carotid body is increased during anoxia.

Dripps and Comroe (1944) divide the drugs that affect the sensibility of the carotid body in two groups: those that, like cyanides and sulfides, produce effects by inhibiting intracellular respiratory enzymes, and those which, like lobeline, are synaptotropic and consequently affect the transmission of afferent impulses. Hollinshead and Sawyer (1945) conclude from the above facts that a chemical agent mediates in the excitation of the carotid body. They suggest that this agent would not be acetylcholine.

Not only are there differences in intensity between the reflex effects of anoxemia and those of central origin, but there are also differences in the speed of the response. This is shown by the frequently cited observations of Heymans, Bouckaert and Dautrebande (1930), of Gemmill, Geiling and Reeves (1934), and of Henderson and Greenberg (1934). These authors observed that the respiration is not increased during the first 4 to 60 seconds of asphyxia due to oxygen-lack produced by breathing pure nitrogen after denervation of the carotid sinus; but that if the asphyxia is continued the hyperpneic reaction appears in the second minute. Carbon dioxide contained in the blood also stimulates the vascular chemo-receptors. In this case however no dominance of the chemo-receptors over the centers is observed. Heymans, Bouckaert and Dautrebande (1930) were able to show that the respiratory response to the breathing of air with CO_2 is produced in the same manner after denervation of the carotid sinus as in the normal state. Gemmill and Reeves (1933); Stella (1935); Wright (1934–36); Gesell and Moyer (1937) demonstrated also intense respiratory reactions to CO_2 after denervation. On the contrary Selladurai and Wright (1932); Schmidt (1932); Green and De Groat (1935); Euler and Liljestrand (1936) observed that with denervation the responses to CO_2, like those to anoxemia, are reduced although never to such a great extent.

It is probable that the differences in the results are due to various factors, the species of animal and the anesthesia. Marshall and Rosenfeld (1937); Comroe and Schmidt (1938); Schmidt and Comroe (1940) believe that the reflexes play a

more important part in anesthetized animals than in those in the normal state precisely because of the effect of the anesthetic on the centers. And they add (1941): "We did not believe that chemo-receptor reflexes are an important factor in maintaining eupneic respiration or in bringing about the respiratory response to carbon dioxide under ordinary conditions." They believe that respiratory centers are more sensible to carbon dioxide than chemo-receptors are.

Gayet, Bennati and Quivy (1935) found intense hyperpnea when the carotid sinus was perfused with equal parts of blood and Locke's solution and the CO_2 tension was increased in the perfusion fluid, but they consider that the effect of CO_2 on the centers is stronger than on the chemo-receptors. Bernthal (1938) and Comroe and Schmidt (1938) state that the reflex effects of the concentration of CO_2 in the blood are less marked, less constant and less well maintained than those produced by anoxemia. Schmidt, Comroe and Dripps (1939) affirm that the threshold of carotid sensitivity to CO_2 is relatively high and always above the threshold of the centers, at least in vagotomized dogs under light anesthesia. Schmidt, Dumke and Dripps (1939–40) confirm this finding; Comroe (1939) points out the existence of marked individual differences in this respect.

Heymans, Bouckaert and Regniers (1933), Gesell (1939) and Schmidt, Comroe and Dripps (1939) agree that great increases in the concentration of hydrogen ions in the blood stimulate the chemo-receptors as strongly as anoxia and more than hypercapnia. Boycott and Haldane (1908) attributed the hyperpnea of anoxemia to an accumulation of lactic acid in the centers. Winder, Bernthal and Weeks (1938) observed an increase in the respiratory movements when the vessels supplying the carotid body were ligated, and after removal of the ligature the hyperpnea and the hypertension disappeared.

Bernthal (1938) perfused the carotid sinus and concluded that in the normal state the carotid chemo-receptors are the origin of tonic vasoconstrictor and respiratory reflexes of great sensitivity which are controlled by the tensions of oxygen and carbon dioxide in the blood. After this Bernthal and Weeks (1939) showed that cooling the blood perfusing the sinus depresses the respiratory and vascular reflexes while warming the blood increases them; they attribute these effects to variations in the acid-base equilibrium of the receptors related to their metabolism. Stadie, Austin and Robison (1927) have already demonstrated the increase in acidity in the tissues as a result of warming.

Schmidt, Comroe and Dripps (1939), and Schmidt, Dumke and Dripps (1939–40) have repeated the experiments of Bernthal using a saline perfusion fluid instead of blood, and carefully determining the concentration of CO_2 and O_2 as well as the pH of the solution. They confirm the results of Bernthal and Weeks but they attribute the effects of the temperature changes to modifications in the gas content of the blood. Winder (1942) perfused the carotid sinus with heparinized blood in Locke's solution which carried CO_2 and O_2 in different concentrations. The effects of hypoxia and of hypercapnia are similar. The chemo-receptors are considered as one of several probable sites for mutual facilitation of hypoxia and hypercapnia acting as stimuli of respiration. Marshall and Rosenfeld (1937) obtained prolonged excitation of the sino-aortic receptors upon in-

jecting pyruvic acid cyanohydrin, probably due to slow, prolonged liberation of cyanide.

The most effective agent for the excitation of the centers and of the chemo-receptors, as Gesell has maintained since 1925, would be a change in the concentration of hydrogen ions in the neurones themselves when the internal environment, the blood or interstitial fluid, becomes acid or particularly when changes in the metabolism flood the neurones with acid metabolites. Warming, ischemia of the sinus or local poisoning with cyanides or sulfides all act in this way. Winder (1942) agrees that intracellular concentration of hydrogen ions is a factor in the control of chemo-receptor activity. Gesell, Krueger, Gorham and Bernthal (1930) examined some time ago the circumstances which can change the concentration of hydrogen ions in the tissues in relation to the insufficient supply of oxygen and the state of their metabolism. They suggest that impaired oxidation leads to increased acidity and that the reverse may also be true.

Bernthal (1938) has shown that anoxia, cyanide, hypercapnia and lactic acid cause reflex peripheral vasoconstriction through their local action on the carotid body, and the vascular reactions are accompanied by respiratory reactions. There is an exact correspondence between the activity of the chemo-receptors and their acidity. Nevertheless the respiratory effects of changes of the hydrogen ion concentration in the carotid body should not make us overlook the sensibility of the respiratory centers to these changes. Moyer and Beecher (1942) assert that decreased oxidations within the center constitute an important factor of respiratory adjustments due to changes in the central pH. This was confirmed by Comroe (1943). He applied upon the respiratory medullary center minute amounts of CO_2-bicarbonate mixtures and observed marked respiratory responses according to the pH of the mixtures. Garcia Banús, Corman, Perlo and Popkin (1944) found that in anesthetized dogs deprived of their chemo-receptor reflexes by the denervation of the carotid sinus and section of both vagi nerves, the respiratory compensation by the centers may be efficient enough to maintain the pH of arterial blood constant at least within 0.01 even if changes of O_2 and CO_2 tension occur in the inspired air.

Gesell (1939) shows that changes in pH in the nerve cells act in the same sense and in the same way in the respiratory centers and in the chemo-receptors: both are sensitive to carbon dioxide and to oxygen lack and hence to externally caused variations in the hydrogen ion concentration, but they are specially sensitive to variations in hydrogen ion concentration of internal origin brought about by the cellular metabolism. As a result of this central and peripheral sensitivity to hydrogen ion concentration, an adjustment is established between the nutritive requirements, the respiration and the circulation.

A characteristic example of these mechanisms of co-ordination is what Hess (1917) has called the "nutritive reflex" which has local and general vascular effects, as Fleisch (1938) and Rein (1938) among others have proved. It is known that any increase in metabolic activity raises the cardiac output. The most effective of the stimuli which give rise to these reflexes of nutritive origin is the acidity of active tissues.

Besides, as Gibbs, Gibbs, Lenox and Nims (1943) wrote, CO_2 improves the oxygenation of the tissues when the O_2 tension in air is low, which enhances the importance of hydrogen ion concentration in cells and in fluids, assuring fine respiratory adjustments from centers to tissues.

Nielsen (1936) suggests in opposition to the idea that the ordinary stimulus of the chemo-receptor centers is the increased local acidity, that carbon dioxide acts by virtue of specific properties and not because it is an acid. CO_2 is said to be the normal stimulus for the respiration: a chemical stimulus produced without interruption in the organism, the principal functional mediator in maintaining the physiological tone of the most diverse functions, especially the circulation and the respiration.

IV. As a result of the simultaneous action on the centers and on the chemo-receptors and as a result of the differences in excitability of centers and receptors depending upon the chemical stimuli acting upon them, various explanations have been developed for the adaptation of the respiration to the changing physiological needs. It is a difficult problem and in certain respects, as it often happens, an imaginary one. The opinions of authors differ in attributing preponderance to the peripheral factors or to the central ones in each case and greater or less physiological significance to the one or the other.

Haldane and Priestley (1935) point out the exquisite sensitivity of the respiratory centers to CO_2, which has long been known. Jongbloed (1936) schematizes the respiratory control stating that carbon dioxide excites the centers directly, while low tensions of oxygen cause tonic excitation of the chemo-receptors, particularly those of the sinus, from which impulses arriving at the centers sensitize them by lowering their functional threshold. Nielsen (1936), Henderson (1938) consider similarly that variations in oxygen to the point of anoxemia control the central activity which is set in motion by the presence of CO_2 in the blood. The tension of oxygen present affects the local action of CO_2 in the respiratory centers.

According to Bernthal (1938) the sensitivity of the carotid body to CO_2 is more variable than its sensitivity to oxygen, and decreases in the presence of an excess of oxygen. The normal tension of CO_2 in the blood exerts a tonic action on the function of the respiratory and circulatory centers by way of the chemo-receptors. Schmidt (1932) stated that the participation of the reflexes from the sinus in maintaining the respiratory movements is to be inferred from the marked reduction or abolition of the respiratory response to anoxemia after denervation of the sinus. But the respiratory reflexes of the sinus are essential only in the case of hyperpnea due to anoxia; apart from this defensive reaction, they do nothing which could not be done without them through changes in the blood flowing through the centers. Sensitivity of the cells of the center to the tension of CO_2 or to the concentration of hydrogen ions in the arterial blood is greater than the sensitivity of the carotid body. The nervous centers take precedence as the most highly specialized part of the mechanisms which control the adjustment of the respiration.

Schmidt insists once again (1941): "The part played by chemo-receptor reflexes in adjusting pulmonary ventilation to the requirements of the body must be negligible under normal conditions. This is indicated by the undoubted facts that the hyperpnea of exercise is not associated with any change in the blood that could stimulate these structures; and that the hyperpnea of carbon dioxide inhalation has not been found to be modified in any measurable way by removing the chemo-receptor influence.... The place of these reflexes in the body's economy lies, not in their sensitivity to factors which... normally regulate breathing, but in their ability to withstand and to respond under adverse circumstances which seriously interfere with the functional capacity of the central neurons. By virtue of this ruggedness, the chemo-receptors are enabled to set up a powerful reflex drive and thus to maintain the activity of the neurons when the latter have lost their ability to respond to their normal stimuli.

Comroe and Schmidt (1938) consider also that the regulation is brought about by the tensions of CO_2 and oxygen in the blood bathing the centers and particularly by the concentration of hydrogen ions resulting from the equilibrium between the two gases. The chemo-receptors, which are more sensitive to oxygen-lack than to excess of CO_2, operate only when the deviations in one or the other or both of the two respiratory gases in the internal environment are very great and without sufficient effects on the centers.

Schmidt, Dumke and Dripps (1939) have made comparative studies of the sensitivity of the centers and of the carotid body to changes in the tension of CO_2 in the blood. The respiratory movements are not altered significantly nor does the tension of CO_2 in the arterial blood change after denervation of the carotid bodies so long as the animal is breathing sufficient oxygen. The carotid reflexes play an important part only in extraordinary circumstances and not concerned with the fine control of the respiration.

Gesell and Moyer (1937) made an experimental study of the central and peripheral factors which determine the frequency and depth of the respiratory movements. Lack of oxygen in the inspired air, and therefore in the alveolar air, causes a very obvious increase in the ventilation. This increase is not prevented by section of both vagi nor by section of the pulmonary fibres of the vagus and denervation of the carotid sinus, leaving the cardio-aortic region sensitive and active. Denervation of the sinus facilitates rather than prevents the acceleration, but it reduces the tidal volume. On the other hand denervation of the carotid and of the cardio-aortic region leaving the pulmonary vagus intact favors the acceleration produced by oxygen-lack. Complete denervation of the chemo-receptors of the sinus,the cardio-aortic area and the vagal pulmonary area eliminates the hyperpnea due to anoxia. It is evident that the lack of oxygen affects the chemo-receptors more than the centers. Hypercapnia acts in a different way: it causes a type of hyperpnea which is characterized principally by increase in the depth of respiration. The denervation of the vascular chemo-receptors, with or without vagal block, does not cause visible changes in this hyperpnea; this indicates that excess CO_2 exerts a stronger dominant stimulation upon the

centers than upon the peripheral receptors. From this equilibrium between the function of the centers and that of the receptors there results the adaptation to the various circumstances which can influence the respiration.

Schmidt and Comroe (1940) are still concerned with the functions of the carotid and aortic sensory zones. They reach the conclusion that in the case of anoxemia and of poisoning by cyanide or lobeline, the increase in ventilation is due to reflexes of vascular origin, from the sinus or the aorta. On the other hand, when an increase in CO_2 or in the concentration of hydrogen ions in the blood occurs, the central effect predominates. The reflex factor does not become active until almost the maximal response of the centers has occurred. They suppose that the different circluatory chemo-receptors show a distinct sensitivity to stimuli brought by the blood. Some of them might be active constantly in physiological conditions because of their greater sensitivity; the majority however function successively in increasing numbers only when the level of the stimuli is raised. A definite *quantum* of increase in stimulating activity is necessary to evoke a measurable reflex response corresponding to a definite threshold. The problem of whether the most diverse stimulating agents affect all the receptors or whether there is a specific sensitivity for each group of them has not yet been solved. The scheme proposed by Comroe and Schmidt is kept unchanged: the CO_2, the degree of acidity of the blood and perhaps of the nervous tissue, is the central stimulus and is almost without effect on the vascular chemo-receptors. Oxygen-lack on the other hand is the stimulus for the chemo-receptors which begin to function only in emergency. The same authors believe that the status of the hydrogen ion as a stimulus to centers and chemo-receptors is at present still uncertain. It seems quite possible that the respiratory effects of changes in pH (in so far as they are not referable to corresponding changes in CO_2 tension) are due to chemo-receptor reflexes and not to a direct effect of hydrogen ions on the centers.

Dumke, Schmidt and Chiodi (1941) try once more to elucidate the parts played by the peripheral chemo-receptors of the carotid sinus in the respiratory responses to anoxemia and to hypercapnia. With the animal breathing room air, quietly and without exerting any force, the ventilation rate is not decreased by denervation of the sinus, which demonstrates that in such conditions of repose the reflexes from the sinus play no appreciable part. Twelve per cent oxygen causes slight respiratory acceleration, which is increased when the proportion of oxygen in the gas mixture is reduced to 10 per cent. Denervation of the sinus makes the response to the drop in the inspired oxygen much less obvious. If 3.5 per cent carbon dioxide is added to the mixture containing 10 per cent oxygen, the respiration is increased; this increase is slightly less when the sinus is deafferented. From all this the authors conclude that hyperpnea produced by anoxia is reflex in nature, depending upon the stimulation of the vascular receptors, while the presence of an excess of CO_2 acts rather upon the respiratory centers. Gesell and Lapides (1938) performed an interesting experiment: they determined the duration of the apnea produced by over-ventilation of the alveoli in intact dogs and comparatively after blocking the nerve fibres of the sinus with cocaine.

With the nerves blocked the apnea lasts considerably longer. This means that with the afferent nerve of the sinus no longer conducting impulses and therefore with the chemo-receptors no longer functioning, a lower concentration of oxygen is required to excite the centers.

The observations of Witt, Katz and Kohn (1934) lead us to suppose that the participation of the chemo-receptors in maintaining the respiration is not dispensable. Deafferentation of the respiratory centers by section of the vagi and denervation of the carotid sinus results in depression of the respiration and in some cases in cessation and subsequent death. The impulses which normally reach the centers by the afferent nerves stimulate and condition the activity of the centers, and the respiratory mechanism depends to a great extent on the integrity of the peripheral receptors and its conductory nerves. Finally the authors consider that, in addition to the receptors of the sinus and to those which send their fibres through the vagus (pulmonary and cardio-aortic receptors) still others may play a part in the physiology of the respiration.

The centers and the chemo-receptors act in co-ordination in response to and according to the state of the gas content of the blood. Gesell (1939) asks whether there could be transitory and variable differences in the respective sensitivities and whether for that reason there might be produced physiological variations in control according to the circumstances prevailing in the respiration, which are always variable. Thus the threshold of a given chemical sensitivity would not be constant in a given place either central or peripheral.

If during intense hyperpnea by hypercapnia, the nerves of the carotid sinus are blocked with the vagi blocked as well, no decrease in the respiratory movements is observed at the time when the chemo-receptors should be stimulated most strongly. This could be explained in two ways: 1. The respiratory centers respond more vigorously than the receptors to high tensions of CO_2, while the reverse is true at lower tensions. 2. Hypercapnia is unable to maintain the reflexes in this case because the carbon dioxide in the centers blocks the impulses arriving from the chemo-receptors (Gesell and Moyer, 1935). Thus during intense hypercapnia, central stimulation of the vagus produces no effect on the respiration. It seems nevertheless that asphyxia ordinarily increases the effectiveness of afferent respiratory impulses and that the effects of chemical stimulation predominate in the respiratory centers (Gesell, Moyer and Kittrick, 1942).

There remain functional relations of great complexity between the peripheral receptors and the centers and variations would be possible in the relative participation of the mechanisms which control the functions of the centers and of the various chemo-receptors. Any rigid schema which is proposed in an attempt to explain these complicated phenomena can scarcely conform to all the facts.

V. There still remain other important factors which must be considered in studying the action of carbon dioxide on the centers and on the receptors in controlling the respiration. Not only is hypercapnia important, but also a factor of great influence is the lack of CO_2 sufficient to alter its necessary quantitative relationship with oxygen in the air and in the blood.

Mosso (1885) called attention to the effects of hypocapnia when rarefied air is breathed at high altitudes. Since then many have been carried out, some of which have had immediate practical importance. We refer particularly to the work of Yandell Henderson and his collaborators since 1908.

Hasselbalch (1912), Hasselbalch and Lindhard (1915) and Henderson and Haggard (1918) demonstrated that the ratio $\frac{H_2CO_3}{NaHCO_3}$ is altered by hyperpnea (L. J. Henderson, 1919). The concentration of H_2CO_3 in the blood is reduced by the increased expiration of CO_2 and the alkalosis must be compensated by a reduction in base, principally in fixed alkali, i.e., sodium, which is followed by an increased elimination of ammonia, sodium, etc., in the urine. On the other hand a higher concentration of carbon dioxide causes an increase of alkali in the blood. This has been confirmed repeatedly (Haldane, Kellas and Kennaway, 1919; Davies, Haldane and Kennaway, 1920; Gesell, 1922–23; Gollwitzer-Meyer, 1924; etc). Henderson (1925) and Gesell (1925) have summarized in two excellent reviews what was then known of the chemical regulation of the respiration, referring of course at that time only to the action of chemical stimuli on the centers.

When the respiratory elimination of CO_2 becomes excessive, as in the hyperpnea of anoxia for example, a paradoxical situation arises with increased pulmonary ventilation and simultaneous hypocapnia of the centers, in which the CO_2 is washed out. The more intense the hyperpnea of anoxia with subsequent hypocapnia particularly during anesthesia, the less will be the central control and the greater the peripheral control through the chemo-receptors. Hypocapnia reduces the excitability of the centers (Gesell and Lapides, 1938) and if it remains excessive the centers do not provide adequate ventilation. Anoxia results finally in respiratory depression, which is to be explained by the paralyzing effect, especially on the nervous functions, when the oxygen lacks (Verworn, 1903). The nerve cells are particularly sensitive, more so than any other cells, to anoxia and to asphyxia.

The chemo-receptors are in general strongly excited by degrees of anoxemia which depress or paralyze the physiological activity of the central neurones. But so long as the anoxia of the centers is not excessive the lack of oxygen increases their excitability to CO_2, the normal chemical stimulus. In this way the tension of oxygen in the blood would intervene in the control of the ventilation by its action on the respiratory centers. As the anoxia becomes more severe, asphyxia of the neurones hinders the process of regulation, impeding or even paralyzing the central responses; but at that time the chemo-receptors are still able to respond to the lack of oxygen in the blood and the respiration is maintained by the impulses which they set up as a compensatory reaction. This persistence of the excitability of the receptors leads one to suppose that the metabolic level of the sensory cells which compose them is lower than that of the central neurones.

Gesell (1939) holds to his old point of view: the regulation of the respiration is carried out by the acid-base equilibrium, by the pH in the nerve cell, and not by that in its environment, the interstitial fluid, still less by that in the blood. It

is the acid-base equilibrium of the centers primarily and also of the chemo-receptors. Only by taking into account the state of the acid-base equilibrium, not in the internal environment but in the intracellular fluid itself, is it possible to explain a number of facts which otherwise present insoluble problems.

Acidosis of the blood, for example, is not in all cases an obvious cause of hyperpnea. Henderson (1938) has shown that in carbon monoxide poisoning when there is an increase in the ventilation alkalosis is produced by hypocapnia which up to a certain point protects the centers from the harmful effects of anoxia.

We have seen the significance of the accumulation of acids in the cells of the centers and of the chemo-receptors; acids which arise in the intermediate metabolism of the cells and are also dependent upon the acids of the surrounding fluid, the internal environment. Gesell (1925) has explained how the respiratory centers function to maintain their optimal acid-base equilibrium. McGinty and Gesell (1925) have shown that the concentration of lactic acid in the brain and also in the blood increases when carbon monoxide is administered. The same thing happens in cyanide poisoning and in hemorrhage. Local accumulations of lactic acid and of other acids(pyruvic, citric, etc.) are possible in the nerve centers and other organs, in some cases perhaps without any increase in the acids of the blood.

We can explain now the danger of administering oxygen alone in attempting to combat anoxemia. The oxygen releases quantities of acid, particularly lactic acid, which disappears by oxidation and by resynthesis, and free base remains which binds CO_2, decreasing the normal stimulus for respiration. For this reason in respiration at high altitudes the addition of CO_2 to the inspired oxygen helps to increase the oxygen in the blood, to restore normal respiration and to produce the subjective improvement which is felt with each breath, as has been shown by Schneider, Truesdell and Clark (1926), and by many others, most recently by Dill (1938).

The final conclusion from all that has gone before is that for various reasons—lack of oxygen, excess of CO_2, hemorrhage, the action of certain poisons, and increased temperature in the centers or chemo-receptors—the general acid-base balance of certain organs can be changed and it is precisely the state of this balance which controls the respiration. One must not judge this equilibrium only from the pH of the blood; the local intracellular pH of neurones in the centers and of the sensory cells or neighboring cells in the peripheral chemo-receptors is of greater importance. Various factors act upon these equilibria and only by considering exactly the complex influence of such factors can one explain certain facts which otherwise would seem paradoxical if not contradictory

Schmidt and Comroe (1940) report that many different substances evoke reflexes through their action on the chemo-receptors, particularly those of the carotid sinus. The active substances are of various sorts. We can explain the mechanism of action of some, according to what has already been said, by their influence on the nutrition of receptors through the cellular metabolism; this explanation cannot be applied to others to which we might attribute a

specific action, like that of so many drugs which act on various portions of the autonomic system.

It should be pointed out that the receptors are not only affected by variations in the hydrogen ion concentration, but that they may be excited by a variety of agents foremost among which are normal or accessory products of the intermediate or final metabolism of the tissues. It is possible that there is actually something more in these mechanisms than the regulation of oxidations and the production of acids. It may be that the processes of chemical excitation have greater significance and even though it has not been possible to confirm the mediation of endocrine products of the glomerular tissue in accordance with the hypothesis of Moniz de Bettencourt, Rodrigues Cardoso and Paes de Vasconcellos (1938), it would not be illogical to suppose that the capacity to stimulate the chemoreceptors and the centers extends to various substances of endogenous origin, metabolites or specific substances, "active substances" in the sense used by Demoor. In this way mechanisms of functional correlation and of regulation would be established, as a result of which the respiratory response could be perfectly adapted from moment to moment to the functional metabolic needs, which change rapidly according to the circumstances. Among those chemical stimuli which are able to evoke such mechanisms the most important is the concentration of hydrogen ions in the appropriate tissues.

VI. As long ago as 1876 Latschenberger and Deahna had formulated the hypothesis of the reflex influence of the peripheral circulation on the regulation of the respiration. Recently various investigators have sought by different methods to locate the vaso-sensory zones. Spalto and Consiglio (1886), Hager (1887), Pagano (1900), Siciliano (1900), Brodie and Russell (1900), Mayer, Magne and Plantefol (1920), Frey and Hagemann (1921), Haggard and Henderson (1922), Hess (1923), Tournade and Malméjac (1931), Tournade (1932), Tournade and Rochisani (1934), etc., demonstrated the sensitivity of the vessels and the effects of the chemical excitations which occur in them. The stimulation of these vascular receptors has effects which are predominantly circulatory, but which are inseparably linked to respiratory effects. Among these reflexes particular interest attaches to the respiratory reflexes which are produced by variations in the pulmonary circulation as a result of the stimulation of receptors in the vessels, as observed by Harrison, Harrison, Calhoun and Marsh (1932), Schwiegk (1935) and Christie (1938). Waele and Van de Velde (1940) describe respiratory reflexes through cardiac receptors.

In the same way receptors are found in various organs the excitation of which results in respiratory reflexes. Lewy (1891), Varaldi (1893), DuBois-Reymond and Katzenstein (1901–02), Baglioni (1903), Fleisch (1921), Scott, Gault and Kennedy (1922) have repeatedly confirmed the existence of such reflexes evoked by the excitation of sensory endings of the muscles. The most obvious effect is obtained from the diaphragm and from other respiratory muscles (Fleisch, 1928–30; Hess, 1931; Sharpey-Schafer, 1932; Gesell, 1935). Krogh and Lindhard (1917) produced respiratory reflexes upon faradic stimulation of various groups

of muscles. These effects may be similar to those which are observed when any sensory nerve capable of causing pain is stimulated.

The metabolic state of the tissues and particularly of the muscular system may therefore produce reflexes. It is well known that the respiratory activity increases automatically when the work is increased; this is due to central processes but still more to nutritive reflexes, reflexes which one may suppose are organized to constitute systems,—sometimes very extensive systems,—of respiratory reflexes. Because the increase in respiration begins at the same time if not before the commencement of work, Krogh and Lindhard (1920) thought that this was a matter of central effects, of efferent irradiation in connection with the muscular excitation from the centers (Paterson, 1928). Allen (1942) describes respiratory effects as responses to conditioned reflexes. All this presupposes the existence of reflexogenic receptors in the organs. Harrison, Harrison, Calhoun and Marsh (1932) and Harrison (1939) state as a result of their experiments on dogs and their observations of healthy and diseased human beings that reflexes evoked by movements of the legs help to produce the hyperpnea of exercise. Alam and Smirk (1937) showed the existence of a chemo-sensitive system in the muscles which is capable of evoking vasomotor reflexes as a result of the accumulation of metabolites produced in exercise. Comroe and Schmidt (1943) confirm the possibility of other similar respiratory reflexes resulting in hyperpnea and evoked by movements of the legs. These reflexes are thought to be elicited by excitation of the muscular chemo-receptors which are sensitive to inorganic metabolites, especially carbon dioxide. These mechanisms were suggested long ago by Volkmann (1841) and by Vierordt (1844).

Schmidt and Comroe (1941) and Comroe (1944) assert that in the hyperpnea of exercise the respiratory adjustment depends on receptions in the muscles, lungs (Christie, 1938; Harrison and others, 1939) and perhaps in the heart (Waele and Van de Velde, 1940), besides many other well-known important factors.

The stimulation of chemo-receptors in the active tissues has been conclusively demonstrated as has their effect on the circulation and the respiration. We have referred above to the nutritive reflexes. Through their mediation the cardiac output arises as the metabolic exchange in the tissues is increased.

The regulation of the vegetative functions becomes progressively comprehensive until resulting in generalized responses. Thus, reversing the relationship stated above, respiratory stimuli affect the circulation in an entirely appropriate fashion. The addition of CO_2 to the inspired air increases the blood flow in the brain and decreases it in the muscular system as has been demonstrated repeatedly by Schmidt (1928) in the cat, Lennox and Gibbs (1932) in man, Irving and Welch (1935) in the rabbit, and Irving (1939) in the beaver and the muskrat. Bernthal (1934) observed that when the carotid sinus was perfused with blood containing oxygen at a tension 10 mm. Hg below the normal there is a reduction in the blood flow through the axillary artery. An increase in the CO_2 tension of the blood increases the flow. Section of the vagi makes these effects more obvious.

From all this it is to be concluded that the respiration like the circulation is controlled from the organs themselves by the presence of chemical stimulating substances. We have shown (1941) that a reflex increase in the respiratory movements is produced by asphyxia of the trunk when it has been isolated from the head and separated therefore from the carotid sinus and when the heart has been denervated, inactivating the cardio-aortic chemo-receptors. This effect can only be the result of the stimulation through CO_2 of receptors located in the lungs or in the tissues or in both regions.

VII. Afferent impulses of the most diverse origin produced by the excitation of receptors of all sorts reach the respiratory centers. Besides stimulation of mechanic and chemo-receptors, the stimulation of other more or less specific receptors is important. In the first place we may note the stimulation of many sensory nerves which evoke respiratory reflexes. Painful sensations can retard or accelerate the respiratory movements depending upon the circumstances (Henderson, 1910, Meyer, 1914). Proprioceptive sensations coming from muscles and proprioceptive sensations of position from muscles, joints and labyrinths affect the respiratory movements. Stimulation of the special senses of sight, hearing and smell and of the sensory endings for cold and heat result in changes in the respiration. This is true also of impulses from the autonomic regions. Centripetal impulses which affect the respiration may come from the whole organism by all pathways.

One must not forget on the other hand the automaticity of the respiratory centers which can maintain up to a certain point alternate inspiration and expiration in the absence of any external influence. This was suggested by Legallois (1812), and recognized later by a large number of investigators (Langendorf, 1888; Schrader, 1887; Lewy, 1891; Lewandovski, 1896; Foa, 1909–11; Winterstein, 1911; Scott and Roberts, 1923; Roberts, 1925; Adrian and Buytendijk, 1931; Finley, 1931; Barcroft, 1934, and many others).

The anatomical localization of the respiratory centers and their functioning have been studied intensively. Flourens supposed that they are located near the tip of the "calamus scriptorius," and Gierke that they are made up of cells connected to the fasciculus solitarius. Mislavski (1885), Aduco (1890) and recently Henderson and Sweet (1929), Finley (1931), Henderson and Craigie (1936), Nicholson (1936), Nicholson and Brezin (1937), Nicholson and Sobin (1938) search the localization of the respiratory centers in the medulla. Worthy of special comment is the paper by Gesell, Bricker and Magge (1936) who studied the electric changes in the function of the medullar respiratory centers. These authors, like Brookhart (1940), state that the neurones which make up the bulbar centers are found more or less scattered through the reticular formation. Pitts, Magoun and Ranson (1939) and Pitts (1940–42) attempt to give a precise anatomical and physiological description of these myelencephalic centers. They distinguish in the cat an "inspiratory area" situated in the ventral reticular formation below the inferior olive, and another dorsal, "expiratory area", somewhat higher, extending beyond and bending over the cephalic portion of the inspiratory area. Excitation of one or the other gives rise respectively to contraction of the muscles of inspiration or of expiration.

There are different physiological categories of centers, the higher centers integrating the function of the lower. This is known since the researches of Markwald (1887–90), Loewy (1888), Langendorf (1888), Luscher (1899), Lewandovsky (1896), etc. Thus Lumsden (1923) and later Stella (1938–39), among others, thought that there is a regulator center in the pons—"pneumotaxic"—which has predominant inhibitory properties and so it is able to control the function of the other subaltern centers. Rijlant (1932), who studied the efferent respiratory electric discharges, established a functional hierarchy among the respiratory centers, possessing different specific properties and located in the medulla and the pons. These centers are not compact nor do they form a strict entity but rather a system of adjacent groups of neurones among which those which have thus far been localized experimentally are of particular functional importance.

In the centers the impulses of various origins are integrated and organized. Motor patterns are formed through the synthesis of the most numerous and various elements and these patterns or functional systems give rise to efferent impulses to the muscles and also to other higher centers both subcortical and cortical, which work in unison and in perfect adjustment with the bulbo-pontile centers.

For a long time it has been supposed that the inspiratory-expiratory alternation was a sequence of reflexes started at the vagal ends of the lungs and related to mechanical stimulus: the state of pulmonary inflation or deflation. The discovery of the Hering-Breuer effect (1868) led to a conception universally accepted. The explanation appears by now incomplete. Expiration, like inspiration, can be active. And side by side with the mechanical stimulation of peripheral receptors should be considered the function of chemo-receptors in different territories, and the intrinsic properties of the respiratory centers at various levels of the neuro-axis, especially the medullo-pontile centers.

Bronk and Fergusson (1935) employ the inscription of the electric "fusillades" by the motor nerves to study this question. They conclude that both inspiration and expiration are active and that the rhythmic impulses of excitations arise automatically in the centers, even in the absence of afferent impulses arriving to them. Gesell (1940), Gesell, Magee and Bricker (1940) and Gesell, Atkinson and Brown (1940) describe the patterns of the electric variations in the respiratory motor nerves; inspiratory impulses present there different patterns from the expiratory ones. These experiments show also that the centers are active in inspiration and expiration and that centrifugal currents may leave such centers independently of any afferent impulses. In the respiratory mechanisms there are centrogenic excitations beside reflexogenic influences. The centers maintain a tone and send out rhythmical impulses over the centrifugal pathways; but they are subject to numerous afferent sensory influences of varied origin and nature, and subject also to their own chemical state and that of the blood passing through them.

Gesell and Hamilton (1941) have made a further study of the reflex mechanism by stimulating three types of nerves: the vagus which they consider proprioceptive, the carotid sinus nerve, chemoceptive, and the saphenous, nociceptive; they

confirm the opinion that the two forces which control the respiration are the activity of the central neurones and the influence exerted on the function of these neurones by afferent impulses arising in receptors of various sorts. The sum total of the influences both central and peripheral which at times interfere and at other times re-enforce each other constitutes the power which drives the central nervous system. An overall summation of these different influences is brought about, an organization which the authors attempt to schematize and by means of which the nervous control of respiration is explained. Gesell and Atkinson (1943) deal with the "motor integration" of the respiration still using the analysis of the respiratory discharges in the diaphragm, in various species of animals. In the centers elementary phenomena are integrated which may possibly be identical or similar along the zoological scale and which become complicated in various ways according to the level of function.

Pitts, Magoun and Ranson (1939) study the functional interrelation of the different respiratory centers in the cat employing the Horsley-Clarke technique. There are in the medulla inspiratory and expiratory bilateral groups of neurones, and fibres of the vagus are connected with them. Pitts (1942) reaches the conclusion that four subsidiary systems are present in the medulla: a, an excito-motor center which sends out periodic discharges; b, a vagal inhibitory system; c, a cerebral inhibitory system, cortico-hypothalamic; d, other excitatory and inhibitory systems. The inhibitory systems, both vagal and cerebral, check the activity of the neurones of the motor system and in this way rhythmical respiration is produced; it is also possible that they vary the rate and depth according to need.

Comore (1944) writes recently: "Probably the most important discovery of the last century has been the realization that respiration is controlled not by stimulation of the medulla alone, neither by reflexes alone, but by proper interaction of both factors. No reflex, no matter how strong, can stimulate respiration if the arterial CO_2 tension has been lowered abnormally (Krogh and Lindhard, 1913; Stella, 1939); no chemical stimulant, no matter how great, can produce rhythmic breathing if the medullary centers have been completely cut off from all nervous influence including that residing in pneumotaxic center (Stella, 1938). Respiratory alterations in general cannot be explained by a single theory but only by a consideration of a number of known and probably many unidentified factors. This has been our thesis, a long time ago, since our initial researches.

We cannot finish without stressing the participation of certain cortical regions in maintaining and adapting the respiratory movements to physiological requirements. Consider for example the adaptation of the respiration to the requirements of spoken language. It is not surprising that speaking as well as silent reading (Bellido, 1922), rhythm (Japelli , 1906; Coleman, 1920), various psychic effects (Allen, 1929–42), emotion and finally consciousness and the will all influence the respiratory movements. Fulton (1943) asserts that the regulation of the respiratory movements is a problem of general physiology in the widest sense. A broad concept of the function will keep us from attributing excessive importance to a few isolated facts and from concluding that extremely simple

and limited mechanisms, such as reflexes divorced from the function of the whole, can determine by themselves the flexible respiratory dynamics. Everything which leads to the recognition of new facts is important. But let us not advance an explanation of the whole, which depends upon innumerable factors, in terms of one elementary function—one receptor, one center and one effector. Investigations which have been carried out without a logical conception of the totality of the neural organization and of the adaptation of the responses have contributed to the obscurity of the conclusions and to a general disorientation. The physiologist must be a careful experimenter, but he must have above all a clear idea of what he is seeking; he must attribute to his observations their exact significance and he must know how to incorporate his results into the general theory.

Therefore when we contemplate in the proper perspective the history of the fundamental discoveries in the physiology of respiration we are surprised at the extreme pains taken by some authors to deny the existence and function of chemo-receptors in the respiratory apparatus. Our purpose in studying this problem was motivated by a leading idea expressed in the thesis of Turró (1914), which stated the functions of a "trophic sense" of chemical nature possessed by many different tissues. After the demonstration of the trophic reflexes of hyperglycemia (Pi-Suñer, 1917) and hyperlipemia (Geelmuyden, 1923; Wertheimer, 1926), it seemed to us that it would be an interesting problem to determine whether a reflex mechanism responsive to peripheral chemical stimuli also acts to control the respiratory movements, which are so easily observed and which offer so much for investigation. The results were positive and the researches of numerous investigators have given a decisively favorable response. From the nose (Allen, 1929; Kerekes, 1935; Deseo and Fodor, 1935) and the larynx and trachea (Lumsden, 1924; Graham, 1939–40) to the tissues themselves," a series of chemo-receptors takes part in the control of the respiratory movements: in the respiratory apparatus at various levels, in the circulatory systems and in other parts of the organism.

The vascular chemo-receptors act effectively in the regulation of the respiratory movements but it cannot be doubted that the location of the chemo-receptors in the respiratory apparatus, at various levels, from the nose to the finest bronchioles and the lungs, is a more strategic one. It is logical to suppose that in mammals, animals which breathe air, receptors in the respiratory apparatus itself have greater functional significance than have vestiges of sensory structures in the vessels, which are useful primarily for respiration in the water (Schmidt, 1938).

Gesell wrote recently: "If ever there was a conviction firmly intrenched in physiology, it was the monopoly of the chemical control of breathing by the respiratory center. . . . *It proved to be one of physiology's outstanding creeds.* . . . It was a shaky foundation upon which all of us worked. So when Heymans, *et al.*, produced hyperpnea by a lack of oxygen or an excess of carbon dioxide confined to the aortic (1924–27) and carotid chemo-receptors (1930–32), *he gave us a new outlook on respiration* for which physiology is deeply indebted. . . . *Both central and peripheral* chemical control were proven to be extremely important."

For over a quarter of a century we have been investigating the functions of the respiratory chemo-receptors. The idea of the rôle of the peripheral chemical stimulation of receptors in the processes of regulation of pulmonary ventilation and respiratory dynamics was enunciated by us in 1918 and at the same time the reflex effects from those stimuli were demonstrated. That year we published our first paper on chemo-receptors in the respiratory apparatus, which control its motor functions, and in 1920 we gave a practical demonstration of the technique employed (the dog with two heads, perfusing the head of the experimental dog with the blood of the donor dog) before the Tenth International Physiological Congress in Paris. Since those first experiments, our research work on this subject has been extensive. Today it is an undisputed truth that *peripheral chemo-receptors* are instrumental in the control and the regulation of the respiratory movements.

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