Afferent Fibers of Cardiovascular and Pulmonary Origins and Their Intrabulbar Connections (A Review)

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Technical progress generally opens up new fields of investigation to doctors and research workers. Thus the development of the catheter-technique, of rapidly reacting gas-analyzers and of spectrophotometry led to an extensive experimental and clinical investigation of cardiopulmonary functions. Hemodynamic and gas exchange mechanisms in healthy and diseased persons are much better understood than 20 years ago. Other fields, however, received less attention. This is especially the case, when appropriate methods for clinical use are not available.

Investigations in man are hardly possible when nervous structures within the thoracic and abdominal cavities should be controlled. In man the sensitivity of receptors and the activity of their afferent fibers to medullary or higher centers can be controlled only by indirect methods. We refer therefore to animal experiments, assuming that general rules as to excitation and conduction of nerve impulses exist in homothermal vertebrates, permitting a transposition to man. Certainly, generally applicable rules exist, but there are numerous exceptions or variations when results obtained in different species are compared. Furthermore, a disease may occur only in man or may not be artificially reproducible in animals. Anatomical differences from species to species and within the species are known, and influence the technical procedure of an investigation as well as the results. It will therefore be necessary to assemble as many data as possible on as many species as possible, in order to formulate general rules which are valid for man too, at least with a high probability.

This review will be confined almost exclusively to experiments on animals, but general deductions are formulated at the end of each chapter. It is the author's belief, that only conjoint anatomical and physiological studies permit real progress. That is why some anatomical studies are discussed in the first chapter, and anatomical references are made in subsequent chapters of a more physiological
character.

The title of the review defines and delimits its extent. Receptor structures and their afferent connection outside the thoracic and cervical region, even if related to the general nervous control of respiration and cardiovascular activity will not be referred to. The organization of respiratory and vasomotor centers will not be discussed to a greater extent, with the exception of their possible connection to afferent structures. The report contains no information on the efferent side of cardiovascular and respiratory reflexes. The following chapters may, however, interest not only the physiologist but also the hospital doctor, as the latter frequently has occasion to observe reflex reactions of cardiopulmonary origin in cases of pulmonary embolism, pulmonary hypertension, pulmonary edema, partial pulmonary hypoxia and coronary disease.

I ANATOMICAL STUDIES

Nerve endings of the pulmonary plexus of the vagus can be found in many species to segregate in three groups, a bronchial, a vascular and a pleural group of nerve fibers. Correspondingly vagal nerve fiber end 1) in the epithelium of the primary bronchi down to the walls of the atria of the lung, 2) in the smooth muscle nerve-spindles of the bronchial musculature and 3) in relation to the smooth muscle cells of the tunica media of the pulmonary artery and the pulmonary vein and their branches. This distribution has been observed in men, dogs, cats, rabbits and mice.

Just below the ganglion nodosum the trunk of the vagus of the cat contains about 30000 to 40000 nerve fibers, of which about 20% are efferent. The nerve is predominantly composed of non-myelinated fibers; the ratio of myelinated to non-myelinated fibers has been estimated to be about 1:3. The myelinated fibres are sensory, 54–64% are motor. The efferent myelinated fibers have their main origin in the medulla, a few might originate in the nodose ganglion.

All the large myelinated fibers (above 12μ) and 40–50% of the smaller ones (below 6μ) are efferent, whereas the great majority of the medium sized fibers (6–12μ) are afferent. Transection of the cervical vagus with subsequent degeneration leaves most of the non-myelinated fibres in the lung parenchyma or the neural terminal net unaffected, indicating postganglionic or sympathetic origin. After excision of the second and third thoracic spinal ganglia the intrapulmonary fibers showed no degeneration phenomena.

Of the different branches of the vagus nerve to the trachea, the lungs and the heart, the laryngeal nerves contain the greatest number of myelinated fibers. In the cat up to 100% of the fibers are myelinated in the right superior laryngeal nerve, and about 50% in the recurrent nerve. The aortic (depressor) nerve is composed of about 450 fibers of which about two-thirds are myelinated. They
divide into two groups of 2 to 6µ and 8 to 12µ fiber size. A cardiac branch of one side may contain up to 3000 fibers, of which about 500 are efferent and pre- dominantely not myelinated. At least as many fibers of a cardiac branch with a range of fiber diameter varying from 1 to 12µ are of an afferent nature. The total number of fibers in all bronchial branches of the vagus nerve of one side is about 6000. Of these about 1000 are efferent. The fiber size varies from 1 to 14µ diameter. After supranodal vagotomy only 200 to 300 of the myelinated fibers in the bronchial branches (all below 4µ) degenerate, indicating a high percentage of myelinated fibers of an afferent nature in these vagal branches.2)

The phrenic nerves of cats contain few afferent fibers, i.e. about 10%, of which 80% are of smaller diameter than 5µ.70) Recent studies undertaken at the Physiological Institute of Zürich indicate an even lower percentage of afferent fibers in the phrenic nerve of the rabbit. In the rabbit this nerve is composed of over 90% myelinated fibers, variable in size from 4 to 14µ diameter (Yasargil, to be published). They derive in the cat from endorgans of the Golgi type at the musculo-tendinous junction of the diaphragm.35)

In comparison to the aortic branch of the vagus nerve the carotid sinus or Hering's nerve contains in the cat 650 to 700 medullated fibers. Over 80% of these come from baroreceptor endorgans and measure 6-8µ (3.5%) or 3-5µ (79%). The fibers from the glomus caroticum measure 1.5µ to 2.8µ in diameter and contribute up to 20% of the carotid branch of the glossopharyngeal nerve.33)

Evidence of other reflexogenic zones of the baroreceptor type—besides the sino-aortic region—has been given in the cat.19,17,97) Tenso-receptors in the adventitia were found at the bifurcation of the common carotid artery and the subclavian artery and along the common carotid artery, mainly on the right side. The afferent "depressor" fibers join the aortic nerve. The literature on the anatomy of the arterial baroreceptors and the chemoreceptors has recently been reviewed by Heymans and Neil and by Neil, and the reader is referred to these reviews for further details.

The anatomical studies indicate a rich innervation of the tracheobronchial tree and of both the arterial and venous side of the pulmonary vessels. The greater part of the vagal fibers is of an afferent nature. These may anatomically be divided roughly into two groups, a group of large myelinated fibers (about 30%), and a group of small, poorly or non myelinated fibers. The smallest afferent fibers come from chemoreceptor endorgans.

Anatomical studies give information as to the afferent or efferent nature of nerve fibers only, but not as to their physiological function. The control of dysfunction after severage or temporary blockade of nerves, the artificial stimulation of their central or peripheral stump, and the control of their activity on physiological stimulation with action-current measurement allowed a better understanding of the part which these nerves play in the reflex control of
cardiovascular and respiratory mechanisms. These methods will be treated in subsequent chapters, but first a review of the classification on a functional basis will be given.

II CLASSIFICATION OF CARDIOVASCULAR AND PULMONARY AFFERENT FIBERS

The former classification of sensory fibers of pulmonary and cardiovascular origins in pulmonary stretch receptors (Hering-Breuer vagal afferences) sino-aortic baroreceptors (Blutdruckregler) and aortic and glomic chemoreceptors has to be enlarged on the basis of newer electrophysiological and pharmaceutical studies.

1. Sufficient evidence has been presented to admit that the pulmonary stretch-receptors involved in the reflex regulation of respiration are of two or three types in respect to their mode of activation. 2. Besides the aortic arch, the left atrium, the pulmonary artery at its bifurcation and probably the right atrium at the entrance of the superior and inferior vena cava possess tenso-receptor organs responding to intravascular pressure or volume variations. Such receptors have been defined as atrial, pulmonary and venous receptors. As most of the more recent information is based on action current investigations in combination with artificial stimulation of the receptors or on reflexes elicited by electrical stimulation of afferent fibers, these investigations will now be discussed.

III ACTION CURRENT STUDIES

1. Pulmonary stretch-receptors

It is nearly 100 years since Hering and Breuer and Breuer published their classical studies on "Die Selbststeuerung der Atmung durch den nervus vagus". From the increase of the amplitude and the decrease of the rate of the respiratory movements after bilateral vagotomy and from the reactions to the occlusion of the trachea (later called "Trachealverschlusreaktion nach Head") these authors concluded that the vagus mediates reflexes reinforcing the inspiratory activity when the volume of the lungs is reduced or activating expiratory forces when the lungs are inflated. To this more dynamic concept of the vagal control of respiration Hess, working on hyperventilated apneic animals, added his theory of the control of the diaphragmatic tonus through the vagi.

The first to follow action currents in isolated fibers of the vagus in relation to normal, dyspneic and other forms of breathing were Adrian and Partridge. They noticed during quiet breathing a frequency increase of afferent impulses during inspiration and a decrease during expiration. A maximum of over 200 impulses per second was measured by Adrian after inflation of the cat's lung.

With slow increase of the pulmonary volume up to 50 ml/sec. the tracheal pressure and the impulse frequency in vagal stretch fibers show a striking parallelism. Rapid, repetitive positive pressure ventilation with inflation volumes
higher than 70 ml/sec. leads to an initial maximum of the afferent impulse frequency. But after one second a constant frequency in direct relation to the volume is obtained, variable, however, from receptor to receptor. The pulmonary stretch receptors of the cat are more sensitive to the absolute value of the inflation volume than to its variations in time. This is another demonstration of the tonic nature of afferent information mediated through stretch-receptors.\textsuperscript{31} Conduction velocities ranging between 8 and 44 meters per second were determined for single units of vagal stretch fibers,\textsuperscript{79} and two groups of stretch fibers may be distinguished, slowly and rapidly adapting to stretch stimulation.\textsuperscript{79,112} The afferent fibers concerned with respiratory regulation belong to the A-group, and have an impulse duration of 0.5 to 0.8 millisecond, when derived from the whole vagus trunk.\textsuperscript{58} A differentiation of the active fiber-type in the vagus trunk has been tried by partial blockade of the nerve, either by pressure\textsuperscript{63} or by cold block.\textsuperscript{135} After selective cooling of the vagus stretch fibre activity drops out between 18 and 12°C if single units are controlled headward of the thermode.\textsuperscript{127}

As to the site of the pulmonary stretch receptors nothing definite may be said. In the rabbit 60% of the stretch receptor discharge disappears when the visceral pleura is anesthetized with procaine.\textsuperscript{132} This seems not to hold for the cat, as stripping off larger part of the visceral pleura does not abolish the reactions to lung inflation.\textsuperscript{140} More probably the receptors lie in the tracheobronchial tree\textsuperscript{137,138} or in the bronchioles\textsuperscript{138} or even in the respiratory atria.\textsuperscript{115}

Depending on the speed and the amount of inflation of the lungs the reaction may not always be reflex inhibition of inspiratory activity. Rapid filling of the lungs with large volumes may give rise to a brief inspiratory reaction, called the "paradoxical effect."\textsuperscript{61} This reflex is probably initiated by smaller fibers in the vagus, as this reflex disappears only after cooling the vagus trunk below 6°C.\textsuperscript{139}

The frequently discussed "deflation" or "collapse afferents"\textsuperscript{4,79} have probably only little physiological significance. They may be activated when a pneumothorax is set, or when violent negative pressure breathing is performed or when Veratridine or other amidines are given intravenously.\textsuperscript{31,116} In dogs and cats these amidines may induce an inhibition of respiratory activity which is abolished by vagotomy or by cooling the vagus nerves to below 3°C. Under Veratridine the impulse frequency in vagal stretch fibers increases but the receptors show faster adaption.\textsuperscript{98}

Changes in responsiveness of the pulmonary stretch receptors with consequent change in afferent activity play a major part in respiratory adaptation to pulmonary congestion,\textsuperscript{94,131} inhalation of volatile anesthetics or phosgene.\textsuperscript{20,134} The mechanisms of respiratory and circulatory adaptation to pulmonary embolisms or congestion are extremely complex and certainly not only reflex in nature.\textsuperscript{49}

However, in the cat, pulmonary venous congestion gives a mean increase of
discharge rate of stretch-receptors of about 20% and enhances the Hering-Breuer inhibitory reflexes to lung inflation.\(^{94}\)

2. Other receptors possibly involved in the proprioceptive regulation of respiration

Proprioceptive regulation—besides the vagal mechanisms—might play a part in phasic and tonic adaptational reactions of the respiratory muscles. At first one would look for afferent fibers from the main respiratory muscle (the diaphragm) in the phrenic nerves\(^{22}\). In the cat only about 10% of the nerve fibers in the phrenic nerve are of afferent origin.\(^{150}\) Slowly adapting units which discharge mainly during expiration when the motor innervation is intact come from the muscle spindles of the diaphragm. They have relatively low threshold to stretch and usually cease to discharge during inspiration. Fewer units discharge exclusively during inspiration, having high threshold to stretch and were taken to be tendon organ receptors.\(^{150-152}\) The receptors discharging during expiration were termed "in parallel". Their afferent fibers may be subdivided into two groups. Large fibers show conduction velocities of over 70 m/sec., smaller fibers between 30 and 60 m/sec. The fibres coming from receptors activated by inspiration (termed "in series") show conduction velocities of 70 m/sec. They belong therefore to group I of muscular afferents. Thus in the cat the proprioceptive innervation of the diaphragm is similar to that of skeletal muscles, but the afferent units are considerably less numerous in the phrenic nerve than in nerves of the limb muscles.\(^{29,151}\) These few afferents have, however, little influence as compared to the vagal stretch-receptors on the respiratory centers as shown in the reflex reaction to tracheal closure after vagotomy.\(^{123}\)

Electrical activity synchronous with respiratory movements may be led off from the cuneate fascicle of the dorsal funiculus and the superficial layer of the dorso-lateral funiculus in the decerebrate cat. Over 60% of the fibers show increasing and decreasing activity throughout the whole respiratory cycle, 26% discharge mainly during inspiration, and 13% mainly during expiration.\(^{149}\) This indicates that other afferents coming probably from respiratory muscles reach the level of the bulbopontine respiratory centers, their origin, however, has to be further investigated. In dorsal roots of cat's thoracic nerve fibers have been picked up discharging either continuously or synchronously with inspiration or expiration. They are not tactile fibers, but only once could the corresponding receptor area of the intercostal wall be circumscribed.\(^{124}\)

3. Cardiovascular baroreceptors

The literature on baroreceptor activity has so tremendously increased in the last years, that the reader may be referred for the older literature to the monograph of Heymans and Neil.\(^{49}\) Two reviews of the afferent impulse activity in cardiovascular receptor fibers have recently been given by Neil\(^{97,98}\) and cover the
Little has since been added to the knowledge of the activation and function of the classical buffer nerves from the sinusal and aortic region. They are already active in newborn and three-week-old rabbits, and action current studies reveal as in adults a linear relation between discharge frequencies in the aortic depressor nerve and the height of the systemic blood pressure.43)

Electrophysiological evidence of baro-receptors in the pulmonary artery have been presented for the dog26,28) and the cat.11) In the cat after denervation of the sino-aortic baroreceptor areas action currents may be led off in the right vagus nerve, which are synchronous with changes in pulmonary artery pressure. The discharge occurs during the systolic rise of the pulmonary arterial blood pressure and clamping of the pulmonary artery causes an abrupt decrease of the discharge rate. The increased pulmonary venous pressure after clamping of the aorta is equally followed by a marked increase of discharge rate. The active fibers in the vagus may be dissected down to a small branch of vagal fibers which leave the main vagal trunk about 2 cm cephalad to the azygos vein.11) In the dog recordings from vagal fibers whose endings were located in the pulmonary artery showed a ventricular systolic pattern of discharge, beginning after the R-peak of the E.C.G.27) No receptors could be found in the trunk of the pulmonary artery. The majority of endings were situated in the right pulmonary artery or in the left branch near the ligamentum arteriosum. Half of the pulmonary arterial baroreceptor fibers were concentrated in just two branches of the vagus nerve, the ventro-medial cervical cardiac nerve on the left and the recurrent cardiac nerve on the right side.28)

Slowly adapting fibers coming from endorgans in the atrial walls of the heart have been intensively investigated since Henry and collaborators44,45) demonstrated that inflation of the atria caused reflex diuresis. In the dog distension of the left atrium by inflation of an indwelling atrial balloon causes an increase in activity of vagal afferent fibers which normally discharge during the v-wave of the left atrial pressure.66,111) The corresponding receptors have been called “volume-receptors” and were considered as the point of origin of the aforementioned diuretic reflexes. In fact several vagal branches to the atria which contain afferent fibers may be found. The salvos registered can be correlated with the waves of the central venous pressure or with the different deviations of the E.C.G. The A-type shows activity during the P-R interval synchronously with atrial systole. The B-type, inactive during atrial systole, discharges synchronously with atrial filling.99) When the heart rate is very low a further activity appears during the T-wave and following P-wave of the E.C.G., which corresponds in time to the atrial venous filling. But depending on the experimental conditions the type A receptor may become B in character and vice versa, at least in the cat.99) In the dog, the impulse pattern depends mainly on the speed with
which the distension of the atria is performed. Impulse frequencies up to 300/sec. have been registered. A good correlation between the activity of fibers of the B-type (endystolic) and the stroke-volume or the speed of atrial distension has been found. In respect to the Henry-Gauer-reflexes the correlation of the sum of impulses per unit of time to the intrathoracic blood-volume may be of more importance than the individual response pattern.

The end-formations of the atrial receptors are situated in the endocardium or the subendocardial layers. Flattened plates parallel to the endocardial surface were formed by the branching of myelinated fibers measuring 3 to 10 μ in diameter.

4. Chemoreceptor afferents from the cardio-pulmonary and the carotid-sinus region

From the extensive literature on carotid body (glomic) and aortic body receptors (reviews) only a few papers will be recalled here, because of their particular importance. Fibers, anatomically controlled as coming from the aortic bodies of the cat, show a considerable increase in the number of afferent impulses visible during diastole when the oxygen content of the ventilation mixture is lowered to 5%. The spikes of fibers active during low oxygen pressure breathing were of the same amplitude and character as the spikes of the smallest pressoreceptor fibers. Lowering the blood-pressure was equally if not more potent than 5% O₂ in inducing this small spike activity, which on the other hand would disappear when pure oxygen was given. The conduction velocity of chemoreceptor fibers in the aortic nerve is estimated to be about 10 m/sec. with a range of 7-12 m/sec. This is a somewhat higher figure than given for the so-called "deflation receptors of the lungs" (6 m/sec.).

Isolated perfusion of the pulmonary artery in cats and rabbits with sodium cyanide added to the perfusion mixture has been used to demonstrate chemoreceptors in the pulmonary artery walls. Small spikes were led off by this technique in the right cardiac vagus. It is probably, therefore, that similar baro- and chemoreceptor structures exist in the aortic and the pulmonary arterial regions.

The glomus caroticum is stimulated by lowering arterial pO₂, increased pCO₂, and severe hemorrhage reducing the blood flow through it. In the latter case stagnant anoxia is the stimulus. The sensitivity of the carotid chemoreceptors to reduction of arterial pO₂ has been studied in cats. It was found that isolated fibers already discharge with pO₂ of 100 or 95 mmHg and a considerable increase in impulse frequency is observed when pO₂ measures 80 mmHg. The arterial pCO₂ threshold has been measured with 30% O₂ in N₂. A linear relationship between pCO₂ and impulse frequency has been determined. The increase of impulses per second is about 30 for an increase in arterial pCO₂ of 10 mmHg. With an arterial pCO₂ of 40 mmHg and pO₂ of 110 mmHg an average of 100 impulses per second may be found in single chemoreceptor
fibers of the Hering's nerve.\textsuperscript{6)}

A quantitative study on chemoreceptor activity was recently undertaken in cats immobilized by Pentobarbitone anesthesia and Flaxedil. Variations of $pO_2$, $pCO_2$ and $pH$ in the arterial blood were used as stimuli for the carotid body, whose activity was measured as integrated action potentials from Hering's nerve after denervation of the carotid sinus baroreceptor zone.\textsuperscript{74)} With this technique the integrated chemoreceptor response at $pCO_2a$ of 40 mmHg ($pH$ 7.21) gave 5 relative units, when $pO_2a$ was 100 mmHg. Lowering $pO_2a$ to 50 mmHg increased the number of units firing to 12 relative units. Further reduction of $pO_2a$ to 30 mmHg activated 25 units. This maximum was lowered to about 12–15 units when $pCO_2a$ was reduced to 16.5 mmHg and $pHa$ increased to 7.55. The authors think to have proven with this experiment a potentiation of the hypoxic stimulus through either $pCO_2$ increase or $pH$ reduction.

From the studies reported in this chapter, it may be summarized that mechano- and chemoreceptor afferents to the respiratory and vasomotor centers may be grouped according to their mode of activation and their function as follows:

1. Pulmonary stretch-receptors discharge mainly in large fibers of the A-group, and respond primarily to lung volume and less to its variations. They have to be considered as tonically active during the whole respiratory cycle with a minimum of activity during expiration. Their intrapulmonary origin, however, is not yet known. Under extreme experimental conditions (rapid inflation of the lungs with large volumes or collapse of the lungs) slowly conducting, small fibers may be activated. These might play a part in reflex-reactions after acute pulmonary edema or pulmonary embolism.

2. Proprioceptive influences from the diaphragm and the thoracic respiratory muscles are less important in respiratory regulation than the vagal stretch-receptors. The phrenic nerve, for instance, contains only 10\% or less afferent fibers.

3. Besides the classical baroreceptor areas of the sino-aortic regions, other baroreceptors have been found in the atria of the heart, at the bifurcation of the pulmonary artery and at the bifurcation of the subclavian artery from the common carotid artery. The baroreceptor impulses are mediated through either large, fast-conducting or small, slow-conducting fibers with a certain dominance of the latter.

4. The slowly adapting receptors of the atria, responding to atrial distension and firing through small vagal fibers, are supposedly at the origin of reflexes for the control of plasma volume. They have been termed "volume receptors".

5. Chemoreceptor afferent fibers belong to the C-fiber group. They are mainly non-myelinated and conduct at low speeds according to their small fiber size. Recently chemoreceptor fibers have been demonstrated to come from the pulmonary artery walls. Aorta and pulmonary artery seem therefore to get a comparable baroreceptor and chemoreceptor innervation.
6. The chemoreceptors are already active at normal pO₂ or pCO₂ in the arterial blood.

Cyon and Ludwig, 1866,⁶⁰ were certainly right to give a prudent title to their first communication on baroreceptors: “Die Reflexe eines der sensiblen Nerven des Herzens auf die motorischen der Blutgefäße.”

Another group of afferents might well interfere with the normal vasomotor and respiratory nervous control. The nociceptor influence on a great number of autonomic activities is well known in clinics. Pain modifies respiration, heart rate and blood-pressure. Therefore, pain afferents should not be neglected in a discussion on cardiovascular and respiratory afferent control.

5. Painfibers of cardio-pulmonary origin

In contrast to the abundant literature on respiratory, baroreceptor or chemoreceptor activity in cervical nerves, the information on nociceptor influx of cardiovascular or pulmonary origin is scanty. The parenchyma of the lungs and the visceral pleura are insensitive to painful stimuli,²¹ but the parietal pleura gets a rich nociceptive innervation from the intercostal nerves.¹³⁴ It is, however, well known that the trachea and large bronchi are sensitive to noxious stimuli, leading in humans to referred plain in the parasternal and substernal region.⁹⁶ An afferent pathway of pain fibers in vagal branches to the trachea and the bronchi is the most probable but a sympathetic pathway has not yet been excluded.⁹⁶

Stimulation of the central part of the diaphragm in man elicits pain referred to the shoulder. In cats under chloralose anesthesia pinching of the diaphragm with forceps or brushing with a solution of 0.5 N acetic acid led to twitches, tail movements, pupillary dilatation and a moderate rise of the arterial blood-pressure.⁵⁶ Such a stimulation of the diaphragm is supposed to activate pain fibers in the afferent phrenic nerve. In contrast to the A-fibre group firing in relation to respiratory movements the pain fibers must be thin fibers of the delta-group or larger C-fibres as revealed by the slowly conducted small spike potentials. Their activity remains unaltered by cooling the phrenic nerve to 4°C.⁵⁶

The mechanism which leads to intense pain in humans after coronary occlusion has been investigated in dogs. In the unanesthetized animal temporary occlusion of the descending branch of the left coronary artery activates or modifies respiration and the animal shows “obvious signs of discomfort”.¹³² These “signs” persist after bilateral vagotomy or after severage of the upper six pairs of intercostal nerves. Bilateral extirpation of the stellate ganglia reduced the reactions to some extent, and they disappeared completely after excision of the 4 upper pairs of the thoracic sympathetic ganglia or after transection of the dorsal roots of the spinal nerves Th 1 to Th 5. Thus the afferent pathway of pain fibers from the heart seems primarily to be sympathetic. However, further in-
vestigations on cardiac pain, making use of the modern electrophysiological technique, would be highly desirable.

IV REFLEX REACTIONS ENGENDERED BY AFFERENT STIMULATION OF VAGAL AND GLOSSOPHARYNGEAL NERVE-BRANCHES

The electrical stimulation of the cranial stump of divided nerves has long since been a widely used investigational tool in order to imitate and to analyze reflex reactions. Already Cyon and Ludwig's discovery of the aortic depressor nerve was based on stimulation experiments. The technique of stimulation has, however, progressed with the technical development, and stimulators delivering electrical shocks of independently variable shock-duration, stimulus strength and stimulus frequency are now commonly used. The exact knowledge of the parameters of the electrical stimulus used is especially important when selective stimulation is tried on fibers with different excitabilities in a mixed nerve such as the vagus or glossopharyngeus. In recent years the afferent stimulation of nerves has frequently been combined with controls of the ascending action currents. This permits one to follow the type of nerve fibers activated and gives a better insight into the nature of the reflex reaction concomitantly observed.

1. Respiratory effects elicited by afferent stimulation of the cervical vagus, superior laryngeal or phrenic nerve

The inspiratory reflexes engendered by deflation of the lungs as observed by Hering and Breuer can also be elicited by electrical stimulation of the cranial stump of the cervical vagus with low frequencies of up to 40/sec. when low intensities are used. The expiratory reactions normally observed when the lungs are inflated may be imitated by afferent vagal stimulation with frequencies from 80 to 200 c.p.s. Wyss in a series of papers presented evidence, that this frequency effect of the vagal stimulation could best be explained by the assumption that the bulbar inspiratory center needed less summation than the expiratory center. Other investigators, using different techniques, however, concluded that the vagus had only inhibitory fibers to the respiratory centers, whereas still others admitted two different kinds of afferent fibers in the vagus, an "acceleratory" and an "inhibitory" group. (For references see). The latter theory is supported by experiments where the afferent vagus is stimulated with progressively increasing intensity. In the rabbit, stimulation (5–20 c.p.s.) of the vagus may first lead to an expiratory reaction which changes with increasing stimulus strength to an inspiratory reaction.

By inspiratory reaction is meant either a shift to bigger expiratory reserve volumes or a prolongation of the inspiratory phase with or without increased tonic reactions. The expiratory reaction is characterized by a reduction of the expiratory reserve volume, a diminution of the resting tone of the diaphragm or a prolongation of the expiratory phase or an arrest of the respiratory movements in expiration.
A detailed description of an experimental analysis of the vagal fibers involved in respiratory control, undertaken by Wyss and Rivkine\textsuperscript{147}) may be given here. This paper clarified several of the older divergencies of opinions: The afferent stimulation of the vagus of rabbits anesthetized with urethane frequently produces slight expiratory reactions when stimulation frequencies from 10 to 40 per second and threshold intensity are used. The fibers thus activated belong to the A-group with conduction velocities from 50 to 70 m/sec. In other cases this initial expiratory reaction is not observed and then a slight increase in intensity will bring into action slower fibers of the A-group which produce a slight inspiratory reaction. When then the frequency of stimulation is increased to 80 or 100 shocks per second the threshold reaction will always be expiratory. On the other hand, when stimulation is continued with 10 to 40 shocks per second, a strong inspiratory reaction coincides with the appearance of a B\textsubscript{1}-wave in the action current picture of the vagus. As long as this B\textsubscript{1}-component is not present, the effect of stimulation frequencies higher than 80 per second will always be purely expiratory. But when B\textsubscript{1}-fibers are activated, mixed expiratory reactions with an inspiratory component are observed. Wyss and Rivkine\textsuperscript{147}) concluded from their experiments, that three sets of afferent fibers are involved in vagal respiratory reflexes. 1. Fast fibers (A\textsubscript{a}) produce a weak expiratory reaction by stimulation with higher frequencies, at lower rates these very fast fibers remain ineffectual. 2. The important group of vagal respiratory afferent fibers consists of somewhat slower fibers of the A-group, comparable to tactile fibers (A\textsubscript{\beta}). They show a characteristic frequency effect. Their low rate stimulation gives rise to a weak inspiratory response with slight breathing acceleration; with increasing frequency, this inspiratory response is converted in an expiratory one, with a marked slowing of respiration. 3. Distinctly slower fibers of the B\textsubscript{1} type are responsible for the strong inspiratory reaction with marked acceleration of breathing and increased inspiratory tone. The authors concluded further, that probably only the faster fibers, showing the frequency effect, play a part in the Hering-Breuer type of respiratory reflexes. They believe that the B\textsubscript{1}-fibers are physiologically activated only when the lungs collapse and that they correspond to "collapse fibers" as first described by Adrian.\textsuperscript{11}) Fibres for the weak inspiratory effect have chronaxic values of 0.1 to 0.2 msec., fibers for the strong inspiratory effect show a chronaxy of about 1.0 msec.\textsuperscript{49)}

Similar results as to dependency of the respiratory reflex on stimulation frequency or intensity have been obtained in cats,\textsuperscript{77,125}) guinea-pigs,\textsuperscript{107,108,109}) monkeys,\textsuperscript{144}) rats,\textsuperscript{78}) rabbits,\textsuperscript{59,60,77}) However, there are differences from species to species. The cat reacts to threshold stimuli applied to the afferent vagus predominantly with expiratory reactions. The guineapig shows mainly inspiratory reactions and a marked increase of frequency to vagal stimulation. In the latter animal the afferent vagus seems indispensable for the maintenance of rhythmic
breathing. In the tracheotomized, otherwise intact or slightly anesthetized animal bilateral vagotomy is followed by a gasping type of breathing with very low respiratory frequencies, leading to death in pulmonary edema after several hours. This can also be produced by cooling the vagi to 2°C. Normal breathing, however, can be maintained in the vagotomized animals by continuous stimulation of the cranial vagal stump.108)

Another vagal branch, the superior laryngeal nerve, when stimulated distally to the junction with the aortic nerve always gives expiratory reactions. They are at threshold purely inhibitory, affecting little the depth of the inspiratory movements. A prolongation of the expiratory phase is usually obtained on which active expiratory movements of the coughing type may get superimposed, when stronger stimuli are used.104) Under physiological conditions these laryngeo-inhibitory fibers on respiration discharge mainly during expiration and are greatly activated by an increase of the intratracheal pressure.5,118,119) The afferent discharges in the superior laryngeal nerve reinforce therefore the vago-inhibitory reactions to lung inflation.

Afferent stimulation of the phrenic nerve produces no systematic influence on the spontaneous respiratory patterns. Increase or decrease of respiratory frequency may be the result.57) When the afferent stump of a dissected phrenic nerve is stimulated and action currents of the intact contralateral phrenic are derived, a crossed inhibition is obtained with threshold stimuli, while with stronger stimuli a contralateral activation is observed.36) Stimulation of the dorsal roots of the spinal nerves C3 to C8 leads to a direct activation of both sides of the diaphragm.123) By increasing the intensity of the stimuli applied to the dorsal roots, the homolateral anterior roots are directly activated, leading to a sharply defined potential 2 msec. after the onset of stimulation. A second or reflex discharge occurs 5 msec. later.

2. Effects on arterial blood-pressure obtained by afferent vagal stimulation

Changes of the mean arterial blood-pressure are considered here as an indication of a variety of cardiac, arterial and venous reactions engendered by artificial stimulation. No attempt will be made to dissociate the efferent components of these reflexes. Other reviews have to be consulted for this purpose.120,129)

In the rabbit the pulmonary stretch-receptor fibers and the aortic baroreceptor fibers have a separate course low in the neck. They can, at will, be stimulated separately or together. A separate aortic depressor nerve is found in cats in about 30 to 50% of the animals, while in dogs these baroreceptor fibers generally join the main vagus trunk. Vagal stimulation at threshold intensity leads in spontaneously breathing rabbits to a reduction of the mean arterial blood-pressure. This depressor effect is primarily independent of the
concomitant inspiratory or expiratory reactions elicited. However, when a prolonged arrest in expiration is obtained, which is frequently the case under barbiturates, the initial fall of the blood-pressure progressively changes to a rise. This is probably due to CO₂ accumulation and the interference of chemoreceptor reflexes.\(^{100}\) Stronger stimuli generally produce a rise of the systemic blood-pressure but the fibers involved have not been analyzed in the rabbit.

In the dog's vagus two, possible three fiber types have been demonstrated to be involved in blood-pressure reflexes elicited by artificial stimulation.\(^{12}\) The fibers of the A and B groups are entirely depressor. Their stimulation leads to a fall in systemic blood-pressure and a decrease of the heart-rate. The C-fiber group is mainly, but not exclusively, pressor. Its activation leads to a reflex cardiac acceleration and a rise of the systemic blood-pressure. With rectangular impulses of 0.13 msec. pulse duration the respective threshold are for A-fibers 0.3-0.5 volts and for B-fibers 0.8-2 volts; for the activation of C-fibers 20 or more volts are needed.\(^{12}\) Differences in species in these responses have to be expected as the vagus nerve of the dog has more C-fibers than the cat's vagus. The vago-pressor fibers are presumably of chemoreceptor origin. The baroreceptor fibers of the aortic arch are faster conducting and belong mainly to the B-group in the dog, or to the A- and B-group in the cat. It may be stressed that no frequency effect could be demonstrated for vagal afferents involved in cardiovascular reflexes, i.e. the increase of the rate of stimulation does not produce a reflex reversal as in the above-described respiratory reactions.

3. **Afferent stimulation of the aortic depressor nerve**

The aortic depressor nerve has best been investigated in the rabbit. This nerve contains fast conducting fibers (A-B-group, 20-40 m/sec. conduction velocity) and slow conducting fibers (poorly or nonmyelinated C-fibers, with 1 m/sec. or less conduction velocity).\(^{39}\) Stimulation of the aortic depressor with 16 to 64 shocks per second leads in this animal to a fall in systemic blood-pressure which develops in two phases, when increasing intensities are used. A first slight depressor reaction is obtained at threshold intensity for the A-B-fibers group, a much stronger effect is produced when the C-fibers are activated with much higher intensities. When stimulation is prolonged sufficiently to cause a maintained depressor response this response is usually independent of the pattern of stimulation. Only at low rates of stimulation (8-32/sec.) the interrupted (more physiological) type of stimulation is slightly more effective than the continuous type.\(^{40,41}\) The central summation of afferent impulses from the aortic baroreceptors seems in these experiments to depend rather little from the pulsatile or not pulsatile inflow-pattern. This is somewhat in contrast to other experiments in which it had been shown that pulsatile increase of the intravascular pressure was more effective in stimulating baroreceptors than continuous and maintained elevated
pressure.

In the cat the aortic depressor nerve contains, besides depressor fibers, also pressor ones, and shows therefore more similarity to the Hering's nerve of the carotid sinus region. In the complex reactions probably 3 types of fibers intervene depending on the stimulus strength used: 1) large depressor fibers (having low threshold, optimal stimulation frequency 60–120/sec.), 2) small pressor fibers (higher threshold, optimal rate of stimulation 10–20/sec.) and 3) still smaller depressor fibers (very high threshold, optimal stimulation frequency between 60 and 125/sec.).

4. Electrical stimulation of Hering's nerve

As the carotid sinus branch of the glossopharyngeal nerve contains afferent fibers from the baroreceptor (sinusal) and the chemoreceptor (glomic) area, its stimulation will normally provoke complex reactions. The author's attempt to stimulate selectively the one or the other fiber-type in the carotid sinus nerve of rabbits was but partially successful. In 60 to 80% of the experiments threshold-stimulation with frequencies of 50 to 100/sec. produces a fall of the systemic blood-pressure without modification of the respiratory activity. The glomic-pressor effects appear when the stimulus-strength is doubled or tripled, and it is more easily obtained with low than with high rates of stimulation. The sinusal fibers respond easily to shocks of 0.02 to 0.1 msec. impulse duration, whereas the glomic fibres are easier to stimulate with longer shocks of 1.0 to 10 msec. impulse duration when impulses of the shape of double condensor discharge are used. However, it is not always possible to separate the two reflex reactions by this method.

Stimulation of the afferent Hering nerve combined with registration of action currents revealed two types of fibers involved in the depressor reflexes. The activation of low threshold fibers of the A-group determines a moderate fall of the systemic blood-pressure. The maximal depressor reaction is obtained with intensities about 20 times higher. High intensity stimulation activates slowly conducting non- or purely myelinated fibers of the C-fiber group. However, when C-fibers are stimulated an activation of the respiration is also observed. This means that glomic fibers have probably been activated together with depressor fibers and that we are already dealing with a mixed reaction, where the depressor fibers have no effect on respiration, and if a respiratory reaction occurs it is an inhibition. On the contrary, electrical stimulation of glomic chemoreceptor fibers with moderate intensities produces a blood-pressure rise accompanied by an increase in inspiratory depth and respiratory frequency. It seems questionable, therefore, whether C-fibers activation in depressor nerves is an advent which is of any importance under physiological conditions of stimulation; they may play the role of emergency regulators, when extreme increase of the aortic or carotid sinus intravascular pressure has to be compensated.
The carotid sinus branch has been stimulated in man.23) A fall of the mean arterial blood-pressure, of the pulse amplitude and of heart-rate were observed, and were best elicited by stimulation frequencies of about 40/sec, when rectangular impulses of 5 msec. pulse-duration were applied through bipolar silver-electrodes. A slight increase of tidal volume and respiratory rate could be observed at the same time. This can best be explained by concomitant activation of chemoreceptor fibers.

Summarizing the results of experiments with afferent stimulation of different branches of the vagus or glossopharyngeal nerve, the following conclusions may be drawn:

1. The respiratory reaction to an afferent stimulation of the cervical vagus depends on stimulus strength and frequency. At threshold, fibers of the A-group are activated. With low frequencies of stimulation respiration will be activated, with higher frequencies inhibited. At about double stimulus strength fibers of the B-group are activated, which leads at lower frequencies of stimulation to a strong inspiratory reaction.

2. The respiratory effect of vagal stimulation show great differences of species. Predominantly inhibitory in cats, the vagal afferents activate respiration in rabbits and guinea-pigs. In the latter animal the dynamogenic action of vagal reflexes is indispensable for the maintenance of adequate breathing rhythms.

3. Stimulation of the superior laryngeal nerve always leads to respiratory inhibition. The results of afferent stimulation of the phrenic nerve are variable.

4. Electrically induced activity of the buffer nerves has little effect on respiration; if any influence occurs, it is inhibitory. Respiratory depth and frequency increase under chemoreceptor influence.

5. The blood-pressure reaction to stimulation of the cervical vagus depends on the admixture of aortic depressor and chemoreceptor fibers. At threshold stimulation the activated A-fibers are depressor fibers, as well as the less excitable fibers in the B-group. Activation of C-fibers leads mainly to pressor reactions.

6. The aortic depressor and the baroreceptor branch to the carotid sinus contain two sets of fibers, both depressor. A slight fall in systemic arterial pressure follows the stimulation of A- and B-fibers. To obtain a maximal depressor effect stimulus strength has to be increased to intensities where C-fibers become activated.

7. Chemoreceptor fibers show high thresholds to stimulation and are all pressor. In some cases a selective stimulation of these fibers in the Hering’s nerve is possible when shocks of longer duration and low stimulation frequencies are used.

8. Stimulation of Hering’s nerve in man is followed by identical respiratory and vasomotor reactions to those in animals.
V THE INTRACRANIAL, PREMEDULLARY AND MEDULLARY PATHWAY
OF CARDIOVASCULAR AND PULMONARY AFFERENT FIBERS

Intracranial sections of the glossopharyngeal and vagal rootlets were performed on rabbits as early as at the end of last century. This was done to determine the origin of the afferent fibers mediating the Hering-Breuer vagal or the aortic depressor reflexes. Both reflexes were abolished when section of the second cranial bundle of the glossopharyngeal-vagal rootlets was carried out.\textsuperscript{9,55) In more recent studies on cats action currents were derived from the dorsal and ventral layers of these rootlets\textsuperscript{8,13) and correlated with simultaneously registered respiratory, blood-pressure or heart-rate manifestations. It can be deduced from these studies, that the cranial and dorsal rootlets contain most of the afferent fibers which fire in relation to heart beat or blood pressure rise. More respiratory active fibers are found in the caudal rootlets. The authors disagree in that von Baumgarten\textsuperscript{8) measures the main respiratory activity in the ventral, Bonvallet\textsuperscript{13) in the dorsal roots of the vagus. The dorsal rootlets may show effenter activity with respiratory rhythms in addition to the more important afferent activity.\textsuperscript{8})

The intrabulbar pathway of afferent fibers of the vagus nerve has been followed mainly with classical methods comprising nerve section and control of fiber degeneration. The central organization of these vagal fibers strikingly resembles the spinal arrangement\textsuperscript{13}, the motor bundles are ventral, the sensory dorsal. In the cat larger sensory bundles pass into the medulla through the more rostral zone and the larger motor bundles though the more caudal zone. The sensory fibers pass through the descending trigeminal tract and enter into the lateral or ventral portion of the solitary bundle. In the rat\textsuperscript{128) degenerating fibers can be traced to all parts of the nucleus of the solitary tract, but the majority terminate in the caudal part of this nucleus. Relatively few fibers cross to the opposite side in the caudal part of the nucleus commissuralis and the caudal most fibers can be traced to the upper part of the spinal cord. A small number of glossopharyngeal and vagal fibers terminate in the small-celled part of the reticular formation, ventrolateral to the nucleus of the solitary tract. Dissection of the rostral rootlets leads to degeneration in the cranial third of the solitary nucleus and caudal to the vicinity of the obex.\textsuperscript{8})

We lack information about the intracentral pathway of fibers mediating impulses from the glomus caroticum. It has been speculated that it is an ascending pathway, but no proof could be given.\textsuperscript{155}

It may be concluded from these anatomical and functional studies that most of the glossopharyngeal afferent fibers end in the fasciculus solitarius or its nuclei. A few fibers may terminate in the spinal portion of the trigeminal nucleus, or in the dorsal parts of the reticular formation. Relatively few fibers descend to the upper cervical levels. The crossing of incoming fibers to the opposite side is not
frequent above the obex level; a larger exchange of fibers from both sides, however, occurs at the nucleus commissuralis. There is a certain grouping of cardiovascular afferent fibers in the cranial and dorsal rootlets and of respiratory afferents in the medial and caudal rootlets.

VI THE MEDULLARY RELAY STATIONS FOR VAGAL RESPIRATORY AND CARDIOVASCULAR REFLEXES

As discussed in chapter V, the afferent glossopharyngeal and vagal fibers can be traced to the solitary tract of the medulla oblongata. It was therefore natural to look for relay stations of the described pulmonary and cardiovascular fibers in the neighborhood of the solitary tract, especially within the nucleus proprius of this tract and the adjacent reticular structures. The studies were primarily undertaken to get a better insight into the organization of the bulbar respiratory centers, but further studies showed that the structures of the solitary tract are only concerned with reflex controls and not with autonomic functions of bulbar respiratory or vasomotor centers.

Referring to our experiments our technique used to localize the relay stations for vago-inspiratory and vago-expiratory or cardio-aortic and sinusal depressor reflexes may be summarized as follows: in rabbits, generally anaesthetized with urethane, the vagus nerves and the aortic depressor nerves of the neck were prepared for afferent electrical stimulation. The carotid sinus was isolated, transformed in a blind-sack by ligation of the common external and internal carotid artery and connected to a syringe for intrasinusal pressure-rise stimulation. The animal was tracheotomized and breathed spontaneously in a spirometer of the Krogh-type. Femoral artery pressure was recorded. The medulla oblongata was exposed and circumscribed areas were either stimulated with electric shocks of variable intensity and frequency or coagulated with high frequency current.

Either bipolar or unipolar electrodes were used. The brain was fixed with formalin and serial sections of 25 or 40μ were stained for cells and fibers.

In a series of about 400 experiments on rabbits a caudally situated “inspiratory” and a cranially placed “expiratory” relay station could first be located on the medial side of the solitary tract. Coagulation in the caudal end of the tractus solitarius abolishes the ipsilateral inspiratory reflexes, but not the expiratory of afferent vagal stimulation. Conversely, the destruction of a small region lying 2 to 3 mm cranial to the obex and at the medio-ventral border of the tractus solitarius suppresses the expiratory vagal reflexes but leaves the inspiratory unaltered. Discrete lesions have to be placed in between these two vagal relay stations at the medial border of the solitary tract, in order to abolish the sino-aortic depressor reflexes, without altering the vago-respiratory ones. The depressor relay stations are found lying just laterally to the promonterium gliosum, and as the other relay stations medially to the solitary tract. The depressor afferences from the carotid sinus are probably relayed in the cranial, those from the aortic region in the caudal part of this “depressor-reflex” center. But no sharp boderline between them may be drawn, and they overlap with the
more cranially situated "expiratory" and the more caudally situated "inspiratory" reflex centers. All three centers are located in a territory occupied by the subnucleus magnocellularis of the solitari nuclei, the lateral parts of the nucleus parvocellularis tractus solitarii, and parts of the nucleus alaris. Effective coagulations frequently include dorsal parts of the nucleus reticularis parvocellularis. However, this latter subnucleus of the medullary reticular formation does not seem to participate in these relay stations as may be inferred from the fact that extensive lesions in the reticular formation below the solitary tract have no influence on the reflexes controlled.

It is interesting to note, that in most experiments where medullary action potentials have been recorded, the solitary fascicule and its nuclei have rarely been investigated when artificially activated by means of physiological or artificial stimulation of the different afferent fibers ending there. Salmoiraghi defines as "cardiovascular" structures nervous elements which fire concomitantly with changes in blood-pressure. Such elements generally show an increased activity when systemic blood-pressure rises, less frequently they react with a reduction of their firing frequency. These elements are grouped neither in the pons nor in the medulla, except in the fasciculus solitarius, but no precise localization is given for the latter case.

Hukuhara et al. controlled in cats the reflex influence of the injection of water in the mouth and of the subsequent deglutition on the activity of respiratory neurones in the medulla. A reflex inhibition or activation mediated by the vagus nerve could be shown, but for technical reasons—the intramedullary pathway of the afferent fibers was not followed. The study of Anderson and Berry which gives more information in this respect will be discussed in the following chapter.

Summarizing the investigations on medullary relay stations, it was found in rabbits that the vago-respiratory and the baroreceptor afferent fibers relay at three different spots.

The relay stations may be called reflex centers, the sequence in cranio-caudal direction is vago-expiratory, depressor and vago-inspiratory. These reflex centers lie at the medial border of the solitary tract and may selectively be destroyed by highfrequency coagulation. The structures which have to be destroyed to get a complete suppression of one of the reflexes without altering the others include the subnucleus magnocellularis and parts of the subnucleus parvocellularis of the solitari nuclei, and parts of the nucleus alaris. Dorsal parts of the medullary reticular formation are frequently included in effective coagulations but seem not to belong to the relay stations.

VII RELAY STATIONS AND BULBAR VASOMOTOR AND RESPIRATORY CENTERS

In continuation of the afore mentioned experiments on vago-respiratory and
sino-aortic reflex centers in the medulla, the same technique of high-frequency coagulation of circumscribed zones was used in a series of experiments with the aim of delimiting the bulbar area, destruction of which would produce primary loss of inspiratory activity, i.e. abolition of respiration in passive expiratory position.\textsuperscript{130} The experiments were performed on rabbits anaesthetized with a mixture of Numal and Urethane. Pneumogramme and femoral artery-pressure were recorded. Bipolar or monopolar electrodes were symmetrically placed in different regions of the medulla. Before coagulation central stimulation was performed to get a gross estimation of the position of the electrodes. The coagulation spots were histologically checked, their relative position to characteristic structures of the medulla determined and their volume measured. With that technique Vassella\textsuperscript{130} got the following results: a group of 14 animals responded after bilateral coagulation with an immediate arrest of all respiratory movements. Another group of 16 animals showed a highly disturbed respiratory activity with frequent gasping and a third group of 50 animals with equally large coagulations in other parts of the medulla had no sign of respiratory disturbance. The author concludes that a nervous structure indispensable for the maintenance of respiration is located in the reticular formation in a region extending from the obex level approximately 2 mm rostrally. The area is defined as lying laterally to the dorsal half of the intramedullary path of the hypoglossus nerve, and beneath the rostral portion of the hypoglossus nucleus. The least active coagulation measured 2.5 mm in a cranio-caudal, 2 mm in a dorso-ventral and 1.5 mm in a mediolateral direction. The more rostrally placed lesions attained the caudal pole of the facial nucleus and the cranial end of the solitary tract. The most caudally placed lesions which produced complete respiratory arrest reached levels of fibres crossing in the cranial part of the lemniscus medialis.

The question arose whether this area had to be considered as an autonomous inspiratory center or whether it would merely represent a zone where descending fibres from higher respiratory centers could be destroyed. Vassella emphasizes that the tractus reticulo-spinalis lateralis and the tractus reticulo-spinalis medialis and ventralis were left intact in a great number of effective coagulations. In addition he observed that the movements of the nostrils stopped after effective destruction of the "respiratory center" at the same time as the thoracic and diaphragmatic movements ceased, and concludes that the coagulations destroyed the primary inspiratory center.

It is not the place here to enter into discussions about the organization of bulbo-pontine respiratory and vasomotor centers. Several reviews on this subject have appeared lately.\textsuperscript{103,104,110} From these the tentative conclusion may be drawn that the medullary respiratory centers are bilaterally organized, have in its medio-caudal parts structures which govern inspiratory and in its cranio-lateral parts others which govern expiratory activity. A vast area of the
medulla certainly contains structures responsible for maintaining a high vascular tone. This area may be called the pressor center, however, little is known about its extent and the nervous elements which participate in its constitution. A small area which has been termed "depressor zone" is found near the obex. It is unlikely that this area exerts an autonomous and continuous inhibitory action on the spinal vasomotor outflow, it is more probable that the "depressor center" coincides with the formerly described relay station for baroreceptor reflexes and that the structures around it are activated by reflex and show no or very little spontaneous activity. ⁹¹,⁹²,¹⁰⁵

The sequence of an expiratory, a depressor and an inspiratory relay station in the cranio-caudal direction was in harmony with the older concepts on the bulbar organization of respiratory and vasomotor centers. In comparison to Vassella's ¹³⁵ "inspiratory center", however, the inspiratory relay structures are found to lie in the rabbit 1 or 2 mm caudal to the caudal end of this area.¹⁰⁶ The expiratory and depressor relay stations lie cranial or just above the central part of the "inspiratory center". The connections through secondary neurones between the relay stations and the proposed inspiratory area are not known as yet, and should be investigated.

As no precise information is available on the location and extent of the bulbar vasomotor center, the depressor relay station cannot be placed in an overall picture of the bulbar vasomotor centers. In Vasella's experiments the coagulation of the "inspiratory center" elicited generally an immediate fall of the femoral arterial pressure, which was followed by an increase in the systemic blood-pressure above precoagulation levels. As respiration stopped a further rise followed before the blood-pressure dropped continuously to very low prelethal levels. This would indicate that the areas in the medulla of the rabbit responsible for maintaining the vasomotor tone do not lie in the "inspiratory area".

In cats, action currents were led off within the medulla during afferent stimulation of the vagus below the superior laryngeal nerve.⁵ Activity was found in intermediulary vagal rootlets as they traverse the spinal trigeminal tract. Action potentials could be recorded in a rostro-caudal area extending through all vagal rootlets down to just rostral to the obex. Action potentials recorded in the tractus solitarius did not show a special grouping, and could be followed in the ipsilateral and contralateral vagal commissure. Upon stimulation of the aortic depressor nerve activity could be traced in the medullary rootlets, the solitary tract and in the sensory nuclei of the ala cinerea. It can be deduced from the reproduced diagrams that the depressor activity occupies regions in the middle of the vagal activity along the solitary tract. No depressor activity was found at the obex level into the vagal nucleus commissuralis. The authors ⁵ consider the neurones in the upper part of the tractus solitarius as primary. In the lower part they admit additional postsynaptic activity. Corresponding to the two fiber
groups forming the peripheral trunk of the aortic depressor nerve, two conduction rates were measured in the aortic afferents. Impulses traveling at 46 and at 8 m per second were found.

These studies confirm the concept that depressor fibers terminate more in the middle part of the solitary fascicule and that vagal fibers may terminate at any height of the solitary bundle. As action currents could be recorded in the nucleus of the tractus solitarius, the parasolitary nucleus, the nuclei of the ala cinerea and the nucleus intercalatus, these nuclei may be considered as terminal stations for the investigated afferent fibers. Coagulations touching these nuclei interrupt—depending on their location—either vago-respiratory or depressor reflexes. They disconnect primary from secondary neurones in these reflex arches.

**In summary, the exact position of the relay stations for vago-respiratory and baroreceptor afferent fibers in relation to the autonomic bulbar respiratory and vasomotor centers cannot be given.**

They lie above a recently described inspiratory center of the medullary reticular formation, but extend more cranially and more caudally than the latter. The impossibility of placing the relative position of reflex and autonomic "centers" is due to the fact that the autonomic centers are not well defined. Afferent stimulation of the vagus and aortic depressor nerve confirms that depressor activity is mainly found in the middle parts of the chain of the solitari nuclei, whereas vagal activity is found over the whole length of the solitary tract and its nuclei.

**VIII THE REGION OF THE OBEEX (AREA POSTREMA)**

Lateral to the obex and medial to the solitary tract lies the relay station for depressor reflexes. The caudal end of the solitary tract can be followed 1 or 2 mm below the obex region. There the inspiratory relay station is found. But the same region has been shown to belong to the vomiting centers in dogs, cats and monkeys. Vomiting could be elicited in the cat by electrical stimulation of the lateral reticular formation in the immediate vicinity of the fasciculus solitarius. In the dog, superficially placed lesions at the obex level with minimal damage to the ala cinerea abolished the emetic response to intravenous apomorphine, but did not suppress the vomiting after oral copper sulphate. Deeper lesions which also involved the lateral reticular formation impaired the responsiveness to oral copper sulphate as well as to intravenous apomorphine. It was concluded that the vomiting center occupies dorsal portions of the bulbar reticular formation and that a trigger zone rendered monkeys less sensitive to X-ray irradiation, cats insensitive to apomorphine given in the fourth ventricle, and dogs less sensitive to uremia following nephrectomy. It is possible that the area postrema and adjacent structures represent a chemosensitive zone. This highly vascularized region at the level of the obex in the floor of the fourth ventricle is
rich in parenchymal cells, and receives fine non-myelinated fibers and thicker fibers from adjacent bulbar regions.\(^{24}\)

In decerebrate, curarized, vagotomized cats, spots could be found just lateral to the area postrema and above or below the nucleus hypoglossi, medial to the nucleus fasciculi solitarii, which show increased electrical activity (spiking) after intra-carotid or intravenous injection of a small amount of hypertonic saline solution.\(^{25}\) Whether the area postrema also represents a sensitive zone to pH and pCO\(_2\) variations\(^{48,89,90,93}\) cannot be decided at present. However, it seems important to note that a possible intramedullary chemosensitive zone lies within the terminal area of afferent vagal fibers.

This region might as well get exteroceptive and proprioceptive influences from the nucleus gracilis and the nucleus cuneatus respectively.\(^{148}\) The importance of such external influences on spontaneously firing respiratory neurones in the cat's medulla could be demonstrated in transection experiments.\(^{122}\) The elimination of supracollicular influences reduced the number of respiratory active neurones which could be detected in the pons and reduced medulla from 100 to 60\%. After subsequent elimination of spinal afferents only 26\% and after additional section of the glossopharyngeal-vagal group about 10\% of the initially firing neurones were found still active.

Not yet understood is the significance of influences on the respiratory or vasomotor centers through afferents from the urinary bladder which end in the obex region. Electrical stimulation of the rostral end of the ala cinerea and cellular masses encircling the solitary bundle at the level caudal to the obex caused contraction of the bladder and rectum in dogs. Stimulation of the reticular formation ventral or ventrolateral to the solitary fascicle just caudal to the obex provoked dilatation and relaxation of these organs.\(^{80}\) On the other hand cellular activity showing changes in discharge frequency synchronous with respiration can be inhibited by means of bladder distension.\(^{81}\)

All this astonishing concentration of afferents in the vicinity of the obex cannot be purely incidental. It is probable that we deal here with a relay area for a great number of reflexes from the thoracic and abdominal viscera. Thus the abandoned term “noeud vital” of Flourens\(^{50,51}\) might become a “vital reflex area”, and the medulla would be seen to be not only the seat of the primary vasomotor and respiratory center, but also to include all primary reflex centers necessary for an adequate regulation of respiratory, cardiovascular and intestinal activity.

*In summary, adjacent structures to the obex and just caudal to it comprise not only the relay stations for vaso-depressor and inspiratory reflexes but also a reflex center for the nervous control of the urinary bladder and the rectum.*

Adjacent structures, especially the area postrema (promontorium gliosum) belong to the vomiting center. Furthermore this area has been thought to function as a central chemoreceptor, however definite proofs for this concept
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are lacking.

As in addition proprioceptive and exteroceptive information converge towards this region, the most caudal part of the fasiculus solitarius seems to terminate in structures which might be considered as a "vital reflex center".

References

9) Beer, Th. & Kreidl, A., Pflügers Arch. ges. Physiol., 1896, 62, 156.
10) Bianconi, R. & Green, J.H., Arch. ital. Biol., 1959, 97, 47, a)
11) Bianconi, R. & Green, J.H., Arch. ital. Biol., 1959, 97, 305, b)
17) Boss, J. & Green, J.H., Circul. Research, 1956, 4, 12.
32) Dawes, G.S., Acta physiol. scand., 1951, 22, 73.
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55) Fuchs, S., Pfliigers Arch. ges. Physiol., 1897, 1897, 117.
87) Larsell, O. & Dow, R.S., Amer. J. Anat. 1933, 52, 125.
Cardiovascular and Pulmonary Afferent Fibers

95) Meier, R., Bein, H.J. & Helmik, H., Experienta, 1949, 5, 484.
1955, 261, 211.